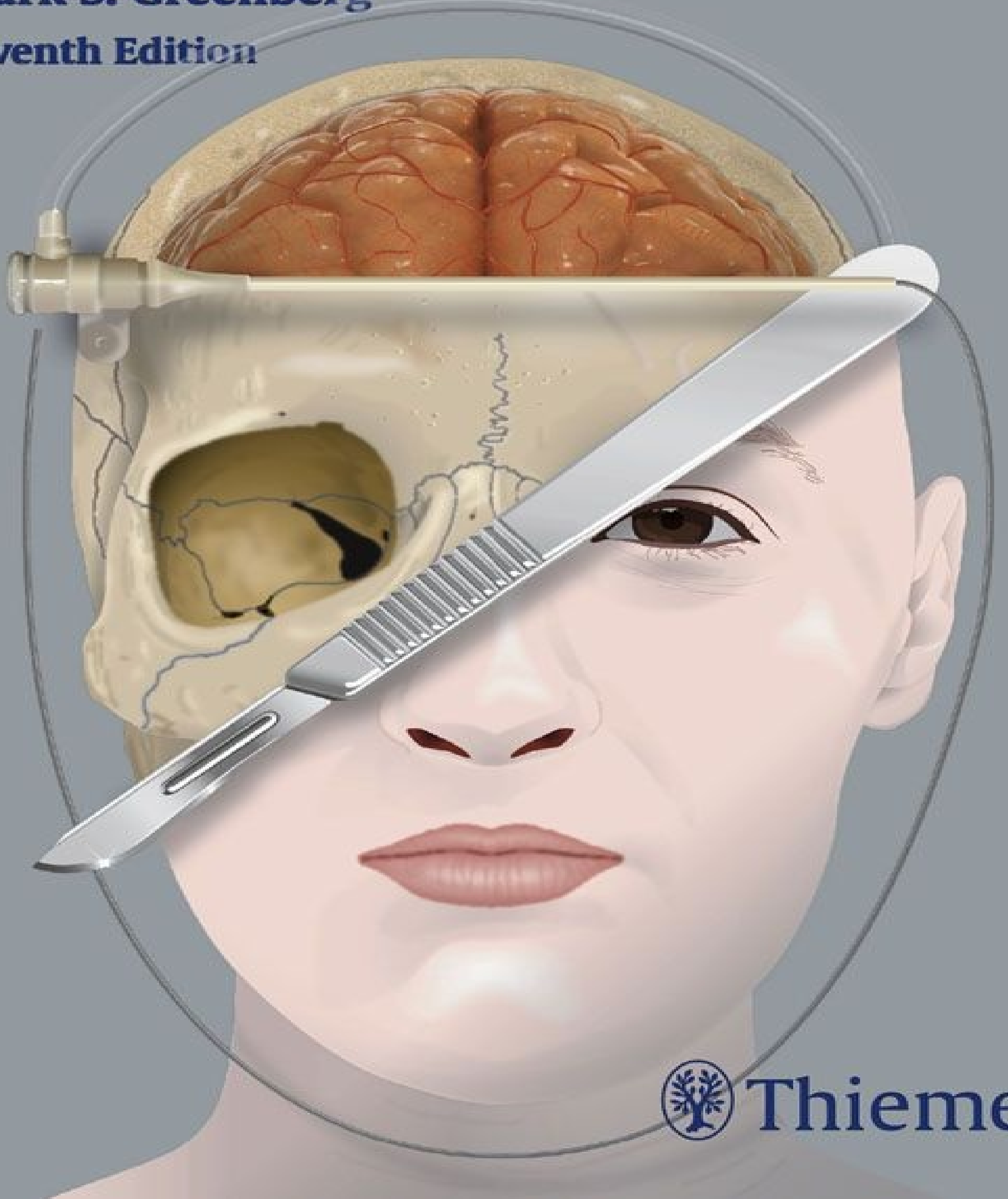
Handbook of Neurosurgery

Mark S. Greenberg

Seventh Edition



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Mark S. Greenberg, M.D.
Assistant Professor
Department of Neurosurgery
University of South Florida
Tampa, Florida

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Thieme Publishers New York
333 Seventh Avenue
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United States of America
Email: customerservice@thieme.com
Tel: +1 800-782-3488 (Toll-free in US only)
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Fax: +1-212-947-0108

In India, Bangladesh, Pakistan, Nepal, Sri Lanka and Bhutan
Thieme Medical and Scientific Publishers Private Limited
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India
Email: customerservice@thieme.in
Tel: +91 120 427 4461 to 4464
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Thieme Publishers Stuttgart
Ruedigerstrasse 14
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CONTRIBUTORS

Naomi A. Abel, M.D.
Electrodiagnostics

Siviero Agazzi, M.D., M.B.A.
Management of vestibular schwannomas
Blunt cerebrovascular injury

Amir Ahmadian, M.D.
Cavernous malformations

Norberto Andaluz, M.D.
Carotid stenosis & endarterectomy
Emergency carotid endarterectomy
Totally occluded carotid artery

Ali A. Baaj, M.D.
Moyamoya disease

Magdalena Banasiak, M.D.
Medulloblastomas & PNETs

Enrico M. Camporesi, M.D.
Introduction to neuroanesthesia
Awake craniotomy

Rafael F. Cardona, M.D.
Bone graft materials

Elias Dakwar, M.D.
CSF fistulas

Armen Deukmedjian, M.D.
Dandy Walker malformation

Angela Downes, M.D.

Spontaneous subdural hematoma

Edward A. M. Duckworth, M.D.
Update on aneurysms, 6ed

Sarah J. Gaskill, M.D., F.A.C.S., F.A.A.P.
Periventricular-intraventricular hemorrhage of the newborn

Shannon Hann
Neurocutaneous melanosis
Treatment of status epilepticus

Michael C. Huang, M.D.
EC/IC bypass
Angiographic pointers

Rashid M. Janjua, M.D.
Peripheral nerve

Tsz Y. Lau, M.D.
Spinal cord stimulators

Shih-Sing Liu, M.D.
Cavernous malformations
Neurofibromatosis von Hippel Lindau disease

Ali R. Malek, M.D.
Stroke

Devanand Mangar, M.D., FCCP
Awake craniotomy

Jotham Manwaring, M.D.
X-linked hydrocephalus

Greg Morris, C.R.N.A., M.S.
Neuroanesthesia

Tann A. Nichols, M.D.
Trigeminal neuralgia, 6ed

Glen A. Pollock, M.D., D.V.M.
PRES
Endovascular neurosurgery

Edwin Ramos, M.D.
Hypothalamic hamartomas

Jaypal Reddy, M.D.
Sagittal balance

Eric Sauvageau, M.D.
Cavernous malformations
Endovascular neurosurgery

Joseph Serrone, M.D.
Pleomorphic xanthoastrocytomas

Juan S. Uribe, M.D.
Bone graft materials
Lhermitte-Duclos disease

Rohit Vasan, M.D.
Subgaleal shunt
Syncope

Justin Whitlow, M.D.
Asymptomatic carotid stenosis

Ashraf Samy Youssef, M.D., Ph.D.
Treatment algorithm for vasospasm, 6ed
Treatment of pineal region tumors

"Seize the moment of excited curiosity on any subject to solve your doubts; for if you let it pass, the desire may never return, and you may remain in ignorance." - William Wirt

DEDICATION

The seventh edition of the Handbook of Neurosurgery is dedicated to my family. To my wonderful wife, Debbie, who's loving support has made this book worthwhile; to my father, Louis Greenberg, for everything he has given me; and to my children, Michael, Leah, Alexa and Shaina.

THE COVER

The scalpel, and more recently, the vascular introducer sheath, are the keys that open the gate to gain access to the nervous system. Illustration by the author. © 2010.

CONVENTIONS

Cross references: the terms "*see below*" and "*see above*" are normally used when the referenced item is on the same page, or at most on the following (or preceding) page. When further excursions are needed, the page number will usually be included.

Σ | Paragraphs with this symbol summarize or synthesizes information from the associated text.

EVIDENCE BASED MEDICINE

The configuration shown below is used to call attention to evidence-based guidelines developed by authoritative committees. The definitions employed are in accordance with generally accepted current usage. The relevant document will be cited. This does not preclude selective deviation from recommendations to individualize care for specific and unique circumstances of a particular case. A standard of care is not implied. For an upto-date listing of some guidelines, visit www.guidelines.gov. If a Level other than I or A is given, this implies that a higher level recommendation could not be made. In some instances, the strength of the data will be mentioned e.g. as (Class II). For a listing of evidence-based guidelines contained in this book, see the *Index* under *practice guideline*.

PRACTICE GUIDELINE: DEFINITIONS	
Strength of recommendation	**Description**

Level I, II, III*	Level A, B, C, D†	
Level I High degree of clinical certainty	**Level A**	Based on consistent Class I evidence (well-designed, prospective randomized controlled studies)
	Level B	Single Class I study or consistent Class II evidence or strong Class II evidence especially when circumstances preclude randomized clinical trials
Level II Moderate degree of clinical certainty	**Level C**	Usually derived from Class II evidence (one or more well-designed comparative clinical studies or less well-designed randomized studies) or a preponderance of Class III evidence
Level III Unclear clinical certainty.	**Level D**	Generally based on Class III evidence (case series, historical controls, case reports and expert opinion). Useful for educational purposes and to guide future research

* as used in the Guidelines for the Management of Severe Traumatic Brain Injury, 3rd edition (Brain Trauma Foundation: Introduction. **J Neurotrauma** 24, Suppl 1: S1-2, 2007).

† as used in the Guidelines for the Surgical Management of Cervical Degenerative Disease (Matz P G, et al.: Introduction and methodology. **J Neurosurg: Spine** 11 (2): 101-3, 2009).

Booking the Case

These sections appear under certain specific operations to help when scheduling that surgery. Default information appears below, for example, a specific type of anesthesia will only be mentioned if something other than general anesthesia is typically used. A list of operations addressed by this means can be found in the index under “Booking the case”. 

Default values: (these details are not repeated in each section).

1. position: (depends on the operation)
2. pre-op:
   A. NPO after midnight the night before except meds with sips of water
   B. antithrombotics: discontinue Coumadin® ≥ 3 days prior to surgery, Plavix® 5-7 d pre-op, aspirin 7-10 d pre-op, other NSAIDs 5 d pre-op
3. cardiology/medical clearance as needed
4. anesthesia: default = general anesthesia, unless otherwise specified
5. equipment: special devices such as ultrasonic aspirator, image guidance…
6. instrumentation: standard surgical instrument trays for a specific operation are assumed. Special instrumentation resident in the hospital will be listed

7. implants: this usually requires scheduling with a vendor (manufacturers representative/distributor) to provide
8. neuromonitoring: will be listed if typically required
9. post-op: default care is on the ward (ICU is typically needed after craniotomy)
10. blood availability: specified if recommended
11. consent (these items use lay terms for the patient - not all-inclusive):
★ Disclaimers: **informed consent** for surgery requires disclosure of risks and benefits that would substantively affect a normal person's decision to have the operation. It cannot and should not attempt to include every possibility. The items listed in this section are included as memory joggers for some items for various procedures, but are not meant to be all inclusive. The omission of information from this memory aid is not to be construed as implying that the omitted item is not important or should not be mentioned.
   A. procedure: the typical operation and some possible common contingencies
   B. alternatives: non-surgical (AKA "conservative") treatment is almost always an option
   C. complications:
      1. risks of general anesthesia include: heart attack, stroke, pneumonia
      2. infection: a risk with any invasive procedure
      3. usual **craniotomy** complications include: bleeding intra-op and postop, seizure, stroke, coma, death, hydrocephalus, meningitis, neurologic deficit related to the area of surgery including (for applicable locations) paralysis, language or sensory disturbances, coordination impairment
      4. usual **spine surgery** complications include: injury to nerve or spinal cord with possible numbness, weakness or paralysis, failure of the operation to achieve the desired result, dural opening which may cause a CSF leak which occasionally needs to be surgical repair. Hardware complications (when used) include: breakage, pull-out, malposition. Although a rare complication, it is serious enough that it bears mentioning in cases positioned prone with possible significant blood loss (> 2 L): blindness (due to PION - *see page 450*)

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ABBREVIATIONS

Abbreviations used only locally are defined in that section using boldface type. Numbers following entries below indicate the page number for the relevant section.

a.	artery (aa. = arteries)
AA	anaplastic astrocytoma - 595
ABC	aneurysmal bone cyst - 728
Abx.	antibiotics
AC	arachnoid cyst - 222
ACA	anterior cerebral artery
ACAS	asymptomatic carotid artery stenosis - 1147 *or* Asymptomatic Carotid Atherosclerosis Study - 1149
ACDF	anterior cervical discectomy & fusion - 462
ACE	angiotensin-converting enzyme
ACh	acetylcholine (neurotransmitter)
AChA	anterior choroidal artery
ACoA	anterior communicating artery
ACTH	adrenocorticotropic hormone (corticotropin) - 111
AD	autosomal dominant
ADH	antidiuretic hormone - 111
ADI	atlantodental interval - 957
ADPKD	autosomal dominant polycystic kidney disease - 1057
ADQ	abductor digiti quinti (or minimi)
AED	anti-epileptic drug (anticonvulsant)- 407
AFP	alpha-fetoprotein - 721
Ag	antigen
AHCPR	Agency for Health Care Policy and Research (of the U. S. Public Health Service)
AICA	anterior inferior cerebellar artery - 104
AIDP	acute inflammatory demyelinating polyra-diculoneuropathy - 67
AIDS	acquired immunodeficiency syndrome - 364
AIN	anterior interosseous neuropathy - 807

AD	autosomal dominant (inheritance)
AFO	ankle-foot-orthosis - 821
AKA	also known as
ALIF	anterior lumbar interbody fusion - 195
ALARA	As Low As Reasonably Achievable - 127
A-line	arterial line
ALL	anterior longitudinal ligament
ALS	amyotrophic lateral sclerosis - 65
AMS	acute mountain sickness - 916
AN	acoustic neuroma - 620
ANA	antinuclear antibodies
AOD	atlantooccipital dislocation - 951
AOI	atlantooccipital interval - 953
AP	antero-posterior
APAG	antipseudomonal aminoglycoside
APAP	acetaminophen - 46
APD	afferent pupillary defect - 831
APTT	(or PTT) activated partial thromboplastin time
ARDS	adult respiratory distress syndrome
ASA	American Society of Anesthesiologists *or* aspirin (acetylsalicylic acid)
ASAP	as soon as possible
AT	anterior tibialis (tibialis anterior)
AT/RT	atypical teratoid/rhabdoid tumor - 688
ASHD	atherosclerotic heart disease
AVM	arteriovenous malformation - 1098
AVP	arginine vasopressin - 111
Ax-LIF	axial lumbar interbody fusion - 195
ß-hCG	beta-human chorionic gonadotropin - 721
BA	basilar artery
BBB	blood-brain barrier - 109
BC	basal cisterns - 909
BCP	birth control pills (oral contraceptives)

BCVI	blunt cerebrovascular injury - 982
BG	basal ganglia
BI	basilar impression/invagination - 138
BMD	bone mineral density - 992
BMP	bone morphogenic protein - 198
BOB	benign osteoblastoma - 736
BP	blood pressure
BR	bed rest (activity restriction)
BSF	basal skull fracture - 887
BSG	brainstem glioma - 607
Ca	cancer
CA	cavernous angioma - 1106
CAA	cerebral amyloid angiopathy - 1122
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAT	(or CT) computerized (axial) tomography
CBF	cerebral blood flow - 1010
CBV	cerebral blood volume
CBZ	carbamazepine - 411
CCB	calcium-channel blocker
CCF	carotid-cavernous (sinus) fistula - 1113
CCHD	congenital cyanotic heart disease
CD	Cushing's disease - 638
CEA	carotid endarterectomy - 1150 *or* carcinoembryonic antigen - 721
CECT	contrast enhanced CT
cf	(Latin: confer) compare
cGy	centi-Gray (1cGy = 1 rad)
CHF	congestive heart failure
CI	confidence interval (statistics)
CIDP	chronic inflammatory demyelinating polyra-diculoneuropathy - 68
CIP	critical illness polyneuropathy - 794
CJD	Creutzfeldt-Jakob disease - 361

CM	cavernous malformation - 1106
CMAP	compound motor action potential (EMG)
$CMRO_2$	cerebral metabolic rate of oxygen consumption - 1010
CMT	Charcot-Marie-Tooth - 793
CMV	cytomegalovirus
CNL	chemonucleolysis - 447
CNS	central nervous system
cCO	continuous cardiac output
CO	cardiac output *or* carbon monoxide - 277
CPA	cerebellopontine angle
CPM	central pontine myelinolysis - 11
CPN	common peroneal nerve - 820
CPP	cerebral perfusion pressure - 866
Cr. N.	cranial nerve(s)
CRH	corticotropin-releasing hormone - 111
CRP	C-reactive protein
CRPS	complex regional pain syndrome - 576
CSM	cervical spondylotic myelopathy - 486
CSO	craniosynostosis - 228
CSW	cerebral salt wasting - 13
CTA	CT angiogram - 128
CTP	CT perfusion - 128
CTS	carpal tunnel syndrome - 808
CVA	cerebrovascular accident (stroke) - 1010
CVP	central venous pressure
CVVT	cerebrovascular venous thrombosis - 1166
CVR	cerebrovascular resistance - 1010
CVS	cerebral vasospasm - 1045
CXR	chest x-ray
DACA	distal anterior cerebral artery
DAI	diffuse axonal injury - 853
DBM	demineralized bone matrix - 199

D/C	discontinue
DDAVP	1-deamino-8-D-arginine vasopressin (desmopressin) - 17
DDx	differential diagnosis - 1185
DBS	deep brain stimulation - 532
DI	diabetes insipidus - 15
DIND	delayed ischemic neurologic deficit - 1045
DIG	desmoplastic infantile astrocytoma and ganglioglioma - 612
DISH	diffuse idiopathic skeletal hyperostosis - 506
DKA	diabetic keto-acidosis
DLC	disco-ligamentous complex - 968
DLIF	direct lateral lumbar interbody fusion - 194
DOC	drug of choice
DM	diabetes mellitus
DMZ	dexamethasone
DNT	(or DNET) dysembryoplastic neuroepithelial tumors - 591
DOE	dyspnea on exertion
DOMS	delayed onset muscle soreness - 478
DPL	diagnostic peritoneal lavage
DREZ	dorsal root entry zone lesion - 575
DSA	digital subtraction angiogram
DSD	degenerative spine - 474
DST	dural sinus thrombosis - 1166
DTs	delerium tremens - 275
DTT	diffusion tensor tractography MRI - 134
DVT	deep-vein thrombosis - 42
DWI	(or DWMRI) diffusion-weighted imaging (MRI) - 132
EAC	external auditory canal
EAM	external auditory meatus
EAST	Eastern Association for the Surgery of Trauma
EBRT	external beam radiation therapy
EBV	Epstein-Barr Virus
ECM	erythema chronicum migrans - 368
EDC	electrolytically detachable coils - 1059

EDH	epidural hematoma - 894
EHL	extensor hallicus longus
ELISA	enzyme-linked immunosorbent assay
ELST	endolymphatic sac tumors - 668
EM	electron microscope (microscopy)
ENG	electronystagmography - 624
ENT	ear, nose and throat (otolaryngology)
EOM	extra-ocular muscles - 834
EOO	external oculomotor ophthalmoplegia
ESR	erythrocyte sedimentation rate
EST	endodermal sinus tumor - 692
EtOH	ethyl alcohol (ethanol)
ET tube	endotracheal tube
ETV	endoscopic third ventriculostomy - 315
EVD	external ventricular drain (ventriculostomy)
FCU	flexor carpi ulnaris
FDP	flexor digitorum profundus]
FIM	Functional Independence Measure - 1184
FLAIR	fluid-attenuated inversion recovery (on MRI) - 129
FM	face mask
FMD	fibromuscular dysplasia - 79
FSH	follicle stimulating hormone - 111
F/U	follow-up
FUO	fever of unknown origin
GABA	gamma-aminobutyric acid
GBM	glioblastoma (multiforme) - 596
GBS	Guillain-Barré syndrome - 66
GCA	giant cell arteritis - 74
GCS	Glasgow coma scale - 279
GCT	granular cell tumor - 641 *or* germ cell tumor - 692
GD	Graves' disease
GFAP	glial fibrillary acidic protein - 720

GGT	gamma glutamyl transpeptidase
GH	growth hormone - 111
GH-RH	growth hormone releasing hormone - 111
GMH	germinal matrix hemorrhage - 1131
GNR	gram negative rods
GnRH	gonadotropin-releasing hormone - 111
GSW	gunshot wound
GTC	generalized tonic-clonic (seizure)
H/A	headache - 57
H&H	Hunt and Hess (SAH grade) - 1039
H&P	history and physical exam
HBsAg	hepatitis B surface antigen
HCD	herniated cervical disc - 461
hCG	human chorionic gonadotropin - 721
HCP	hydrocephalus - 307
HDT	hyperdynamic therapy - 1052
HGB	hemangioblastoma - 667
Hgb-A1C	hemoglobin A1C
hGH	human growth hormone
HH	hypothalamic hamartomas - 226 *or* homonymous hemianopsia
HHT	hereditary hemorrhagic telangiectasia - 1106
HIV	human immunodeficiency virus
HLD	herniated lumber disc - 442
HLA	human leukocyte antigen
H.O.	house officer
HNP	herniated nucleus pulposus (herniated disc) - 442
HNPP	hereditary neuropathy with liability to pressure palsies - 793
HOB	head of bed
HPA	hypothalamic-pituitary-adrenal axis
HSE	herpes simplex encephalitis - 358
HTN	hypertension
IAC	internal auditory canal

IASDH infantile acute subdural hematoma - 899

ICA internal carotid artery

ICG indocyanine green

ICH intracerebral hemorrhage - 1118

IC-HTN intracranial hypertension (increased ICP)

ICP intracranial pressure - 866

ICU intensive care unit

IDDM insulindependent diabetes mellitus

IDET intradiscal endothermal therapy - 448

IEP immune electrophoresis

IG image guidance (intraoperative)

IGF-1 insulin-like growth factor-1 (AKA somatomedin-C) - 111

IIH idiopathic intracranial hypertension (pseudotumor cerebri) - 713

IIHWOP idiopathic intracranial hypertension without papilledema - 714

IJV internal jugular vein

IMRT intensity modulated radiation therapy

INO internuclear ophthalmoplegia - 834

INR international normalized ratio - 39

IPS inferior petrosal sinus

IPA idiopathic paralysis agitans (Parkinson's disease) - 59

ISAT International Subarachnoid Hemorrhage Aneurysm Trial - 1059

IT intrathecal

ITB intrathecal baclofen - 539

IVC intraventricular catheter *or*
inferior vena cava

IVH intraventricular hemorrhage - 1228

IVP intravenous push (medication route) *or*
intravenous pyelogram (x-ray study)

JPS joint position sense

LBP low back pain - 428

LDD Lhermitte-Duclos disease - 593

LE lower extremity

LFTs liver function tests

LGG low-grade glioma - 590

LH	leuteinizing hormone - 111
LH-RH	leuteinizing hormone releasing hormone - 111
LMD	low molecular weight dextran
LMN	lower motor neuron - 786
LMW	low-molecular-weight (e.g. heparins)
LOC	loss of consciousness
LOH	loss of heterozygosity
LP	lumbar puncture - 201
LSO	lumbo-sacral orthosis
MAC	mycobacterium avian complex - 381
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MAST®	military anti-shock trousers
MB	medulloblastoma - 686
MBEN	medulloblastoma with extensive nodularity - 686
MBI	modified Barthel index - 1183
MBS	medulloblastoma - 686
MCA	middle cerebral artery
mcg	(or μg) microgram
MCP	mean carotid pressure *or* metacarpal phalangeal
MDCTA	multidetector CT angiography
MDMA	methylenedioxymethamphetamine - 60
mg	milligram
MI	myocardial infarction
MIB-1	monoclonal anti-Ki-67 antibody - 720
MIC	minimum inhibitory concentration (for antibiotics)
MID	multi-infarct dementia
MISS	minimally invasive spine surgery
mJOA	modified Japanese Orthopedic Association scale - 487
MLF	medial longitudinal fasciculus
MLS	midline shift - 909
MM	myelomeningocele - 248 *or* multiple myeloma - 740

MMD	moyamoya disease - 1170
MMN	multifocal motor neuropathy - 1188
MMPI	Minnesota Multiphasic Personality Inventory
mos	months
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine - 60
MRA	MRI angiogram - 133
MRS	MRI spectroscopy - 133
MRSA	methicillin resistant *staphylococcus aureus*
MS	microsurgery *or* multiple sclerosis - 61
MSO_4	morphine sulfate
MTP	metatarsal phalangeal
MTT	mean transit time (on CT perfusion) - 128
MUAP	motor unit action potential - 270
MVA	motor vehicle accident
MVD	microvascular decompression - 559
MW	molecular weight
n.	nerve (nn. = nerves)
Na	(or Na^+) sodium
N_2O	nitrous oxide - 2
NAA	N-acetyl aspartate - 133
NAP	nerve action potential - 789
NASCET	North American Symptomatic Carotid Endarterectomy Trial - 1150
NB	(Latin: *nota bene*) note well
NC	nasal cannula
NCCN	National Comprehensive Cancer Network
NCD	neurocutaneous disorders - 722
NCV	nerve conduction velocity
NEC	neurenteric cyst - 227 *or* necrotizing enterocolitis
NEXUS	National Emergency X-Radiography Utilization Study - 938
NF	(or NFT) neurofibromatosis - 722
NF1	neurofibromatosis type 1 - 723

NF2	neurofibromatosis type 2 - 724
NG tube	nasogastric tube
NGGCT	non-germinomatous germ cell tumors - 692
NIHSS	NIH Stroke Scale - 1014
NMBA	neuromuscular blocking agent - 25
NMO	neuromyelitis optica (Devic disease) - 1187
NPH	normal pressure hydrocephalus - 329
NPS	neuropathic pain syndrome - 564
NS	normal saline
NSAID	non-steroidal anti-inflammatory drug - 44
NSCLC	non-small-cell cancer of the lung - 704
NSF	nephrogenic systemic fibrosis - 130
NSM	neurogenic stunned myocardium - 1054
NTP	nitroprusside - 19
N/V	nausea and vomiting
NVB	neurovascular bundle
OAD	occipital atlantal dislocation, see atlantooccipital dislocation - 951
OALL	ossification of the anterior longitudinal ligament - 506
OC	occipital condyle
OCB	oligoclonal bands (in CSF) - 65
OCF	occipital condyle fracture - 954
ODG	oligodendroglioma - 609
OEF	oxygen extraction fraction
OFC	occipital-frontal (head) circumference
OGST	oral glucose suppression test (for growth hormone) - 648
OMO	open-mouth odontoid (C-spine x-ray view)
OMP	oculomotor (third nerve) palsy
ONSF	optic nerve sheath fenestration - 718
OP	opening pressure (on LP) - 202
OPLL	ossification of the posterior longitudinal ligament - 504
ORIF	open reduction/internal fixation
OS	overall survival
OTC	over the counter (i.e. without prescription)

PACU post-anesthesia care unit (AKA recovery room, PAR)

PADI posterior atlantodental interval - 495]

PAN poly- (or peri-) arteritis nodosa - 77

PBPP perinatal brachial plexus palsy - 802

$p_{Bt}O_2$ brain tissue oxygen tension - 874

PC pineal cyst- 691

PCA pilocytic astrocytoma - 603 *or*
posterior cerebral artery

PCB pneumatic compression boot

PCC prothrombin complex concentrate - 41

PCI prophylactic cranial irradiation

PCN penicillin

PCNSL primary CNS lymphoma - 672

P-comm posterior communicating artery

PCV procarbazine, CCNU, & vincristine (chemotherapy)

PCWP pulmonary capillary wedge pressure

PDA patent ductus arteriosus

PDN painful diabetic neuropathy - 548

PDR Physicians Desk Reference®

peds pediatrics (infants & children)

PEEK poly-ether-ether-ketone (graft material)

PET positron emission tomography (scan)

p-fossa posterior fossa

PFS progression-free survival

PFT pulmonary function test

PHN postherpetic neuralgia - 564

PHT phenytoin (Dilantin®) - 409

PICA posterior inferior cerebellar artery - 103

PIF prolactin release inhibitory factor - 111

PIN posterior interosseous neuropathy - 817

PION posterior ischemic optic neuropathy - 450

PIVH periventricular-intraventricular hemorrhage - 1131

PLAP placental alkaline phosphatase - 693

PLEDs	periodic lateralizing epileptiform discharges
PLIF	posterior lumbar interbody fusion
PM	pars marginalis - 85
PMA	progressive muscular atrophy - 65 *or* pilomyxoid astrocytoma - 606
PMH	pure motor hemiparesis
PML	progressive multifocal leukoencephalopathy - 364
PMMA	polymethylmethacrylate (methylmethacrylate)
PMR	polymyalgia rheumatica - 77
PMV	pontomesencephalic vein
PNET	primitive neuroectodermal tumor - 686
POD	post-operative day
PPV	positive predictive value: in unselected patients who test positive, PPV is the probability that the patient has the disease
PR	per rectum
PRES	posterior reversible encephalopathy syndrome - 73
PRF	prolactin releasing factor - 111
PRIF	prolactin (releasing) inhibitory factor - 111
PRN	as needed
PRSP	penicillinase resistant synthetic PCN
PSNP	progressive supra-nuclear palsy - 61
PSR	percutaneous stereotactic rhizotomy (for trigeminal neuralgia) - 553
PSW	positive sharp waves (on EMG) - 270
pt	patient
PT	physical therapy *or* prothrombin time
PTC	pituicytoma - 641
PTR	percutaneous trigeminal rhizotomy
PTT	(or APTT) partial thromboplastin time
PUD	peptic ulcer disease
PVP	percutaneous vertebroplasty - 994
PWI	perfusion-weighted imaging (MRI) - 132
PXA	pleomorphic xanthoastrocytoma - 592
q	(Latin: *quaque*) every (medication dosing)
RA	rheumatoid arthritis

RAPD	relative afferent pupillary defect - 831
RASS	Richmond agitation-sedation scale - 23
RCVS	reversible cerebral vasoconstrictive syndrome - 1035
rem	roentgen-equivalent man
REZ	root entry zone
RFR	radiofrequency rhizotomy - 553
rFVIIa	recombinant (activated) factor VII
RH	recurrent artery of Heubner
rhBMP	recombinant human BMP - 199
R/O	rule out
ROM	range of motion
RPA	recursive partitioning analysis
RPDB	randomized prospective double-blind
RPLS	reversible posterior leukoencephalopathy syndrome (see posterior reversible encephalopathy syndrome - 73)
RPNB	randomized prospective non-blinded
RTOG	Radiation Therapy Oncology Group
RTP	return to play (sports) - 851
rt-PA	recombinant tissue plasminogen activator (AKA tissue plasminogen activator)
RTX	(or XRT) radiation therapy - 770
S/S	signs and symptoms
SAH	subarachnoid hemorrhage - 1034
SBE	subacute bacterial endocarditis
SBO	spina bifida occulta - 247
SBP	systolic blood pressure
SCA	superior cerebellar artery
SCLC	small-cell lung cancer - 703
SCD	sequential compression device
SCI	spinal cord injury - 930
SCM	sternocleidomastoid (muscle)
SD	standard deviation
SDE	subdural empyema - 356
SDH	subdural hematoma - 896
SE	status epilepticus (for seizures) - 402)

SEA	spinal epidural abscess - 376
SEP	(or SSEP) somatosensory evoked potential
SG	specific gravity
SIAD	syndrome of inappropriate antidiuresis - 10
SIADH	syndrome of inappropriate antidiuretic hormone (ADH) secretion - 10
SIDS	sudden infant death syndrome
SIH	spontaneous intracranial hypotension - 305
SIRS	septic inflammatory response syndrome
$SjVO_2$	jugular venous oxygen saturation - 874
SLAD	surgical laser aiming device
SLE	systemic lupus erythematosus
SLIC	subaxial injury classification - 968
SMC	spinal meningeal cyst - 509
SMT	spinal manipulation therapy - 438
SNAP	sensory nerve action potential (EMG) - 270
SNUC	sinonasal undifferentiated carcinoma - 1230
SOMI	sternal-occipital-mandibular immobilizer - 979
SON	supraorbital neuralgia - 562
S/P	status-post
SPAM	subacute progressive ascending myelopathy - 1000
SPECT	single positron emission computed tomography (scan)
SPEP	serum protein electrophoresis
sPNET	supratentorial primitive neuroectodermal tumor - 686
SQ	subcutaneous injection
SRS	stereotactic radiosurgery - 773
SRT	stereotactic radiotherapy - 775
SSEP	(or SEP) somatosensory evoked potential
SSPE	subacute sclerosing panencephalitis - 266
SSRI	selective serotonin reuptake inhibitors
SSS	superior sagittal sinus
STA	superficial temporal artery
STICH	Surgical Trial in Intracerebral Haemorrhage - 1129

STIR	short tau inversion recover (MRI image)
STN	subthalamic nucleus
STSG	Spine Trauma Study Group
SUNCT	short-lasting unilateral neuralgiform H/A with conjunctival injection and tearing - 549
SVC	superior vena cava
SVM	spinal vascular malformations - 507
SVR	systemic venous resistance
SVT	supraventricular tachycardia
Sz.	seizure - 394
T1WI	T1 weighted image (on MRI) - 129
T2WI	T2 weighted image (on MRI) - 129
TAL	transverse atlantal ligament - 92
TBA	total bilateral adrenalectomy - 850
TBI	traumatic brain injury - 654
TCA	tricyclic antidepressants
TCD	transcranial doppler - 1048
TDL	tumefactive demyelinating lesions - 64
TE	time to echo (on MRI) - 129
TEE	transesophageal echocardiogram
TEN	toxic epidermal necrolysis
TENS	transcutaneous electrical nerve stimulation
TGN	trigeminal neuralgia - 551
T-H lines	Taylor-Haughton lines - 87
TIA	transient ischemic attack - 1010
TICH	traumatic intracerebral hemorrhage (hemorrhagic contusion) - 893
TIVA	total intravenous anesthesia
TLIF	transforaminal lumbar interbody fusion - 193
TLISS	thoracolumbar injury severity score - 990
TLJ	thoracolumbar junction - 986
TLSO	thoracolumbar-sacral orthosis
TM	tympanic membrane
TMB	transient monocular blindness (amaurosis fugax) - 1144
t-PA	tissue plasminogen activator

TR	time to repetition (on MRI) - 129
TRH	thyrotropin releasing hormone; AKA TSH-RH - 111
TS	transverse sinus
TSC	tuberous sclerosis complex - 725
TSH	thyroid-stimulating hormone (thyrotropin) - 111
TSV	thalamostriate vein
TTP	thrombotic thrombocytopenic purpura
TVO	transient visual obscurations - 715
Tx.	treatment
UBOs	unidentified bright objects (on MRI)
UE	upper extremity
UMN	upper motor neuron - 786
UTI	urinary tract infection
URI	upper respiratory tract infection
U/S	ultrasound
VA	vertebral artery *or* ventriculoatrial
VB	vertebral body
VBI	v]ertebrobasilar insufficiency - 1158
VEMP	vestibular evoked myogenic potential = 624
VHL	von Hippel-Lindau (disease) - 667
VMA	vanillylmandelic acid
VP	ventriculoperitoneal
VS	vestibular schwannoma - 620
VZV	(herpes) varicella zoster virus
WBC	white blood cell (count)
WBXRT	whole brain radiation therapy - 770
WFNS	World Federation of Neurosurgical Societies (grading SAH) - 1040
WHO	World Health Organization. For tumor grading, e.g. WHO II indicates WHO grade II
wks	weeks
WNL	within normal limits
w/o	without
WRS	word recognition score - 623
W/U	work-up (evaluation)

XLIF	extreme lateral lumbar interbody fusion - 194
XRT	(or RTX) radiation therapy - 770

------SYMBOLS------

Rx	prescribing information
→	causes or leads to
Δ	change
✔	check (e.g. lab or exam item to check)
↑	increased
↓	decreased
≈	approximately
⚷	Key concepts
⚡	innervates (nerve distribution)
☞	surgical pointer
⇒	vascular supply
➡	a branch of the preceding nerve
★	crucial point
❏	post-op check item
✖	caution; possible danger; negative factor…
Σ	summary
∴	therefore
www.net	an internet URL address

Medical pearls

Instrumentation: the following short-hand allows rapid identification of metrics for spinal instrumentation

ENTRY screw entry site

TRAJ screw trajectory

TARGET object to aim for

SCREWS typical screw specifications

Contents

1. Neuroanesthesia

1.1. General information

For issues related to intracranial pressure (ICP), cerebral perfusion pressure (CPP), intracranial constituents, etc., *see page 867*. For cerebral blood flow **(CBF)** and cerebral metabolic rate of oxygen consumption ($CMRO_2$), *see page 1010*.

Parameters of primary relevance to neurological surgery that can be modulated by the anesthesiologist:

1. blood pressure: one of the factors that determines CPP. May need to be manipulated (e.g. reduced when working on an aneurysm, or increased to enhance collateral circulation during cross clamping). Measurement by arterial line is most accurate and depending on the patient's presentation and the planned procedure, often should be placed prior to induction of anesthesia. For intracranial procedures, the arterial line should be calibrated at the external auditory meatus to most closely reflect intracranial blood pressure
2. jugular venous pressure: one of the factors that influences ICP
3. arterial CO_2 tension ($PaCO_2$): CO_2 is the most potent cerebral vasodilator. Hyperventilation reduces $PaCO_2$ (hypocapnea) which decreases CBV but also CBF. Goal is generally end tidal CO_2 ($ETCO_2$) of 25-30 mm Hg with a correlating $PaCO_2$ of 30-35. Use with care for stereotactic procedures to minimize shift of intracranial contents when using this method to control ICP[1]
4. arterial O_2 tension
5. hematocrit: in neurosurgery it is critical to balance oxygen carrying capacity (decreased by anemia) against improved blood rheology (impaired by elevated Hct)
6. patient temperature: mild hypothermia provides some protection against ischemia by reducing the cerebral metabolic rate of oxygen ($CMRO_2$) by ≈

7% for each 1° C drop

7. blood glucose level: hyperglycemia exacerbates ischemic deficits[2]
8. $CMRO_2$: reduced with certain neuro-protective agents and by hypothermia (*see above*) which helps protect against ischemic injury
9. in cases where a lumbar drain or a ventricular drain has been placed: CSF output
10. elevation of the head of the patient: lowering the head increases arterial blood flow, but also increases ICP by impairing venous outflow
11. intravascular volume: hypovolemia can impair blood flow in for neurovascular cases. In surgery in the prone position, excessive fluids may contribute to facial edema which is one of the risk factors for PION (*see page 450*)
12. positioning injuries: during the procedure, the patient's position may change and be unnoticed due to draping. Careful and frequent examination of the patient's position may prevent injuries associated with prolonged malpositioning
13. post operative nausea and vomiting (PONV): may adversely affect ICP and may negatively impact recent cervical surgical procedures. Avoidance of anesthetic agents known to cause PONV or pretreatment to prevent PONV may be prudent

1.2. Drugs used in neuroanesthesia

INHALATIONAL AGENTS

Most reduce cerebral metabolism (except nitrous oxide, *see below*) by suppressing neuronal activity. These agents disturb cerebral autoregulation and cause cerebral vasodilatation which increases cerebral blood volume **(CBV)** and can increase ICP. With administration > 2 hrs they increase CSF volume which can also potentially contribute to increased ICP. Most agents increase the CO_2 reactivity of cerebral blood vessels. These agents affect intraoperative EP monitoring (*see page 4*).

nitrous oxide (N_2O) **DRUG INFO**

A potent vasodilator that markedly increases CBF and minimally *increases* cerebral metabolism. Contributes to post-op N/V.

Nitrous oxide, pneumocephalus and air embolism: The solubility of nitrous oxide **(N_2O)** is ≈ 34 times that of nitrogen[3]. When N_2O comes out of solution in an airtight space it can increase the pressure which may convert pneumocephalus to "tension pneumocephalus". It may also aggravate air embolism. Thus caution must be used especially in the sitting position where significant post-op pneumocephalus and air embolism are common. The risk of tension pneumocephalus may be reduced by filling the cavity with fluid in conjunction with turning off N_2O about 10 minutes prior to completion of dural closure. See *Pneumocephalus* on page 890.

Halogenated agents:

Agents in primary usage today are shown below. All suppress EEG activity and may provide some degree of cerebral protection.

isoflurane (Forane®) DRUG INFO

Can produce isoelectric EEG without metabolic toxicity. Improves neurologic out-come in cases of incomplete global ischemia (although in experimental studies on rats, the amount of tissue injury was greater than with thiopental[4]).

desflurane (Suprane®) DRUG INFO

A cerebral vasodilator, increases CBF and ICP. Decreases $CMRO_2$ which tends to cause a compensatory vasoconstriction.

sevoflurane (Ultane®) DRUG INFO

Mildly increases CBP and ICP, and reduces $CMRO_2$. Mild negative inotrope, cardiac output not as well maintained as with isoflurane or desflurane.

Intravenous agents

Induction

Agents generally used for induction:

1. propofol: exact mechanism of action unknown. Short half life with no active metabolites May be used for induction ans as a continuous infusion during total intravenous anesthesia **(TIVA)**. Causes dose dependent decrease in mean arterial blood pressure (MAP) and ICP. For information other than use in induction *see page 3*). Is more rapidly cleared than, and has largely replaced, thiopental
2. barbiturates: produce significant reduction in $CMRO_2$ and scavenge free radicals among other effects (*see page 1063*). Produce dose-dependent EEG suppression which can be taken all the way to isoelectric. Minimally affect EPs. Most are anticonvulsant, but methohexital (Brevital®) can *lower* the seizure threshold (*see page 24*). Myocardial suppression and peripheral vasodilatation from barbiturates may cause hypotension and compromise CPP, especially in hypovolemic patients
   - sodium thiopental (Pentothal®): the most common agent. Rapid onset, short acting. Minimal effect on ICP, CBF and $CMRO_2$
3. etomidate (Amidate®): a carboxylated imidazole derivative. Anesthetic and amnestic, but no analgesic properties. Sometimes produces myoclonic activity which may be confused with seizures. Impairs renal function and should be avoided in patient's with known renal disease. May produce adrenal insufficiency. For information other than use in induction, *see page 3*
4. ketamine: NMDA receptor antagonist. Produces a dissociative anesthesia. Maintains cardiac output. May slightly increase both heart rate and blood pressure.

Narcotics in anesthesia

Increase CSF absorption and minimally reduce cerebral metabolism. They slow the EEG but will <u>not</u> produce an isoelectric tracing. ✖ All narcotics cause dose-dependent respiratory depression which can result in hypercarbia and concomitant increased ICP in non-ventilated patients. Often contribute to post-op N/V

Morphine: does not significantly cross the BBB.

✖ Disadvantages in neuro patients:

1. causes histamine release which
   A. may produce hypotension
   B. may cause cerebrovascular vasodilation → increased ICP[5] (p 1593)
   C. the above together may compromise CPP
2. in renal or hepatic insufficiency, the metabolite morphine-6-glucuronide can accumulate which may cause confusion

Meperidine (Demerol®): has negative inotropic effects, and its neuroexcitatory metabolite nor-meperidine can cause hyperactivity or seizures (*see footnote, page 49*). Also causes histamine release, increased ICP and tachycardia.

Synthetic narcotics

These do not cause histamine release, unlike morphine and meperidine.

⋆ **Remifentanil** (Ultiva®): (*see page 24* for details) reduces $CMRO_2$, CBV and ICP. Large doses may be neurotoxic to limbic system and associated areas. May be used for awake craniotomy (*see page 151*).

Fentanyl: crosses the BBB. Reduces $CMRO_2$, CBV and ICP. May be given as bolus and/or as a continuous infusion.

Sufentanil: more potent then fentanyl. Does not increase CBF. ✖ Raises ICP and is thus often not appropriate for neurosurgical cases.

Alfentanil: the most rapid onset and the shortest duration of the narcotics. ✖ NB: raises ICP.

MISCELLANEOUS DRUGS IN NEUROANESTHESIA

Benzodiazepines: These drugs are GABA agonists and decrease $CMRO_2$. They also provide anticonvulsant action and produce amnesia. See *page 51* for agents and reversal.

Etomidate: Used primarily for induction (*see page 2*). Initial hopes for use as a cerebral protectant were abandoned based on experimental studies[6] and a drop in $p_{Bt}O_2$ with temporary MCA clipping[7]. A cerebrovasoconstrictor, it reduces CBF and ICP. Does not suppress brainstem activity. Suppresses cortisol production with prolonged administration, and may induce seizures.

Propofol: A sedative hypnotic. Useful for induction (*see page 2*). Reduces cerebral metabolism, CBF and ICP. Has been described for cerebral protection (*see page 1064*) and for sedation (*see page 24*). Short half life permits rapid awakening which may be useful for awake craniotomy (*see page 151*). Not analgesic.

Lidocaine: Given IV, suppresses laryngeal reflexes which may help blunt ICP elevations that normally follow endotracheal intubation or suctioning. Anticonvulsant at low doses, may provoke seizures at high concentrations.

Esmolol: Selective beta-1 adrenergic antagonist, blunts the sympathetic response to laryngoscopy and intubation. Less sedating than equipotent doses of lidocaine or fentanyl used for the same purpose. Half life: 9 minutes. For dosing, etc., *see page 20*.

Dexmedetomidine (Precedex®): Alpha 2 adrenergic receptor agonist, used for control of hypertension post operatively as well as, for it's sedating qualities during awake craniotomy either alone or in conjunction with propofol (*see page 151*). Also used to help patients tolerate endotracheal tube without sedatives/narcotics to facilitate extubation.

PARALYTICS FOR INTUBATION

Paralytics (neuromuscular blocking agents **(NMBA)**): administered to facilitate tracheal intubation and to improve surgical conditions when indicated. Administration of paralytics ideally should always be guided by neuromuscular twitch monitoring. Also see *Sedatives & paralytics*, page 23. In addition to paralytics, all conscious patients should also receive a sedative to blunt awareness.

Paralytics should not be given until it has been determined that patient can be ventilated manually, unless treating laryngospasm (may be tested with thiopental). Use with caution in non-fixated patients with unstable C-spine.

Due to long action, pancuronium (Pavulon®) is not indicated as the primary paralytic for intubation, but may be useful once patient is intubated or in low dose as an adjunct to succinylcholine (*see below*).

succinylcholine (Anectine®) DRUG INFO

The only depolarizing agent. May be used to secure airway for emergency intubation, but due to possible side effects (*see page 26*), should not be used

acutely following injury or in adolescents or children (a short acting nondepolarizing blocker is preferred). May transiently increase ICP. Prior dosing with 10% of the ED95 dose of a non-depolarizing muscle relaxant reduces muscle fasciculations.

Rx Intubating dose: 1-1.5 mg/kg (supplied as 20 mg/ml → 3.5-5 cc for a 70 kg patient), onset 60-90 sec, duration 3-10 min, may repeat same dose **x** 1.

rocuronium (Zemuron®) **DRUG INFO**

Intermediate acting, aminosteroid, non-depolarizing muscle relaxant. The only nondepolarizing neuromuscular blocking agent approved for rapid sequence intubation. Duration of action and onset are dose dependent. ***Rx*** *see page 26*.

vecuronium (Norcuron®) **DRUG INFO**

Aminosteroid with activity similar to that of rocuronium, however, does not cause histamine release and is not approved for rapid sequence intubation. ***Rx*** *see page 26*.

cisatracurium (Nimbex®) **DRUG INFO**

Metabolized by Hoffman degradation (temperature dependent), intermediate acting, no significant increases in histamine. ***Rx*** *see page 4*.

1.3. Anesthetic requirements for intraoperative evoked potential monitoring

For details of intraoperative evoked potential **(EP)** monitoring itself, *see page 267*.

All volatile anesthetics produce dose-dependent reduction in SSEP peak amplitude and an increase in peak latency. Adding nitrous oxide increases this

sensitivity to anesthetic agents.

Anesthesia issues related to intraoperative evoked potential **(EPs)** monitoring:

1. induction: minimize pentothal dose (produces ≈ 30 minutes of suppression of EPs), or use etomidate (which increases both SSEP amplitude and latency[8])
2. total intravenous anesthesia (TIVA) is ideal
3. nitrous/narcotic technique is a second choice
4. if inhalational anesthetic agents are required:
   A. use < 1 MAC (minimum alveolar concentration), ideally < 0.5 MAC
   B. avoid older agents such as Halothane
5. nondepolarizing muscle relaxants have little effect on EP (in monkeys[9])
6. propofol has a mild effect on EP: total anesthesia with propofol causes less EP depression than inhalational agents at the same depth of anesthesia[10]
7. benzodiazepines have a mild-to-moderate depressant effect on EPs
8. continuous infusion of anesthetic drugs is preferred over intermittent boluses
9. SSEPs can be affected by hyper- or hypothermia, and changes in BP
10. hypocapnia (down to end tidal CO_2 = 21) causes minimal reduction in peak latencies[11]
11. antiepileptic drugs: phenytoin, carbamazepine and phenobarbital do not affect SSEP[12]

1.4. Malignant hyperthermia

Malignant hyperthermia **(MH)** is a hypermetabolic state of skeletal muscle due to idiopathic block of Ca^{++} reentry into sarcoplasmic reticulum. Transmitted by a multifactorial genetic predisposition. Total body O_2 consumption increases **x** 2-3.

Incidence: 1 in 15,000 anesthetic administrations in peds. 1 in 40,000 adults. 50% had previous anesthesia without MH. Frequently associated with administration of halogenated inhalational agents and the use of succinylcholine (fulminant form: muscle rigidity almost immediately after succinylcholine, may involve masseters → difficulty intubating). Initial attack and recrudescence may also occur post-op. 30% mortality[13].

Presentation

1. earliest possible sign: <u>increase</u> in end-tidal pCO_2
2. tachycardia (early) and other arrhythmias
3. with progression:
   A. coagulation disorder (DIC) (bleeding from surgical wound and body orifices)
   B. ABG → increasing metabolic acidosis & decreasing pO_2
   C. pulmonary edema
   D. elevated body temperature (may reach ≥ 44° C (113° F) at rate of 1° C/5-min) (normal patients become hypothermic with general anesthesia)
   E. limb muscle rigidity (common, but late)
   F. rhabdomyolysis → elevated CPK & myoglobin (late)
4. terminal:
   A. hypotension
   B. bradycardia
   C. cardiac arrest

Treatment

1. eliminate offending agents (stop the operation, D/C inhalation anesthesia and change tubing on anesthesia machine)
2. **dantrolene** sodium (Dantrium®) 2.5 mg/kg IV usually effective, infuse until symptoms subside, up to 10 mg/kg
3. hyperventilation with 100% O_2
4. surface and cavity cooling: IV, in wound, per NG, PR
5. bicarbonate 1-2 mEq/kg for acidosis
6. IV insulin and glucose (lowers K^+, glucose acts as energy substrate)
7. procainamide for arrhythmias
8. diuresis: volume loading + osmotic diuretics

Prevention

1. identification of patients at risk:
   A. only reliable test: 4 cm viable muscle biopsy for in-vitro tests at a few regional test centers (abnormal contracture to caffeine or halothane)
   B. family history: any relative with syndrome puts patient at risk

C. related traits: 50% of MH patients have heavy musculature, Duchenne type muscular dystrophy, or scoliosis

D. patients who exhibit masseter spasm in response to succinylcholine

2. in patients at risk: avoid succinylcholine (nondepolarizing blockers preferred if paralysis essential), may safely have non-halogenated anesthetics (narcotics, barbiturates, benzodiazepines, droperidol, nitrous…)
3. prophylactic oral dantrolene: 4-8 mg/kg/day for 1-2 days (last dose given 2 hrs before anesthesia) is usually effective

1.5. References

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2. Neurocritical care

Neurocritical care topics covered in other sections of the book are shown in *Table 2-1*:

Table 2-1 Neurocritical care topics covered outside this chapter (followed by page number where the item may be found)

Intracranial pressure (ICP) monitoring - 868
Treatment of elevated ICP - 876
Adjuncts to ICP monitoring (jugular venous oxygen, brain tissue oxygenation, microdialysis…) - 874
Neurogenic stunned myocardium - 1054
Status epilepticus - 402
Vasospasm (including triple-H therapy) - 1045

2.1. Fluids and Electrolytes

2.1.1. Electrolyte abnormalities

2.1.1.1. Sodium

HYPONATREMIA

Key concepts:

- definition: serum $[Na^+] < 135$ mEq/L
- minimum W/U: ✔ serum $[Na^+]$, ✔ serum osmolality, ✔ urine osmolality, ✔ clinical assessment of volume status. if volume status is high or low ✔ urinary $[Na^+]$
  - SIADH: hypotonic hyponatremia (effective serum osmol < 275 mOsm/L) with inappropriately high urinary conentration (urine osmol > 100 mOsm/L) and euvolemia or hypervolemia
  - cerebral salt wasting **(CSW)**: similar to SIADH but with extracellular fluid volume <u>depletion</u> due to renal sodium loss (urinary [Na} > 20

mEq/L)

- treatment: based on acuity, severity, symptoms & etiology (see SIADH (*page 11*) or CSW (*page 14*) as appropriate)
- risk of overy rapid correction: osmotic demyelination (including central pontine myelinolysis - CPM)

Classification:

$[Na^+]$ < 135 mEq/L = mild, < 130 = moderate, < 125 = severe hyponatremia.

Hyponatremia in neurosurgical patients is chiefly seen in:

- syndrome of inappropriate antidiuretic hormone secretion (**SIADH**, *see below*): dilutional hyponatremia with normal or elevated intravascular volume. The most common cause of hyponatremia[1]. Usually treated with fluid restriction. May be associated with numerous intracranial abnormalities (*see Table 2-2*) and following transsphenoidal surgery
- cerebral salt wasting **(CSW)**: inappropriate natriuresis with volume depletion. Treated with volume replacement (opposite to SIADH) and sodium (symptoms from derangements due to CSW may be *exacerbated* by fluid restriction[2], *see page 13*). Etiology of 6% of cases of hyponatremia following aneurysmal SAH[3]

Other etiologies of hyponatremia

- renal failure
- volume overload (e.g. as in congestive heart failure)
- **pseudohyponatremia**: osmotically active solutes (e.g. glucose, mannitol, marked hyperlipidemia, or hyperproteinemia (which can occur in multiple myeloma)[4]) draw water from cells and also reduce the water fraction of plasma and produce artifactually low sodium values (an artifact of indirect lab techniques). For every 100 mg/dl increase of glucose, serum [Na] decreases by 1.6-2.4 mEq/L. It is necessary to measure serum osmolality to rule-out pseudohyponatremia

Evaluation

Figure 2-1 shows an algorithm for evaluating the etiology of hyponatremia[5] which drives treatment decisions.

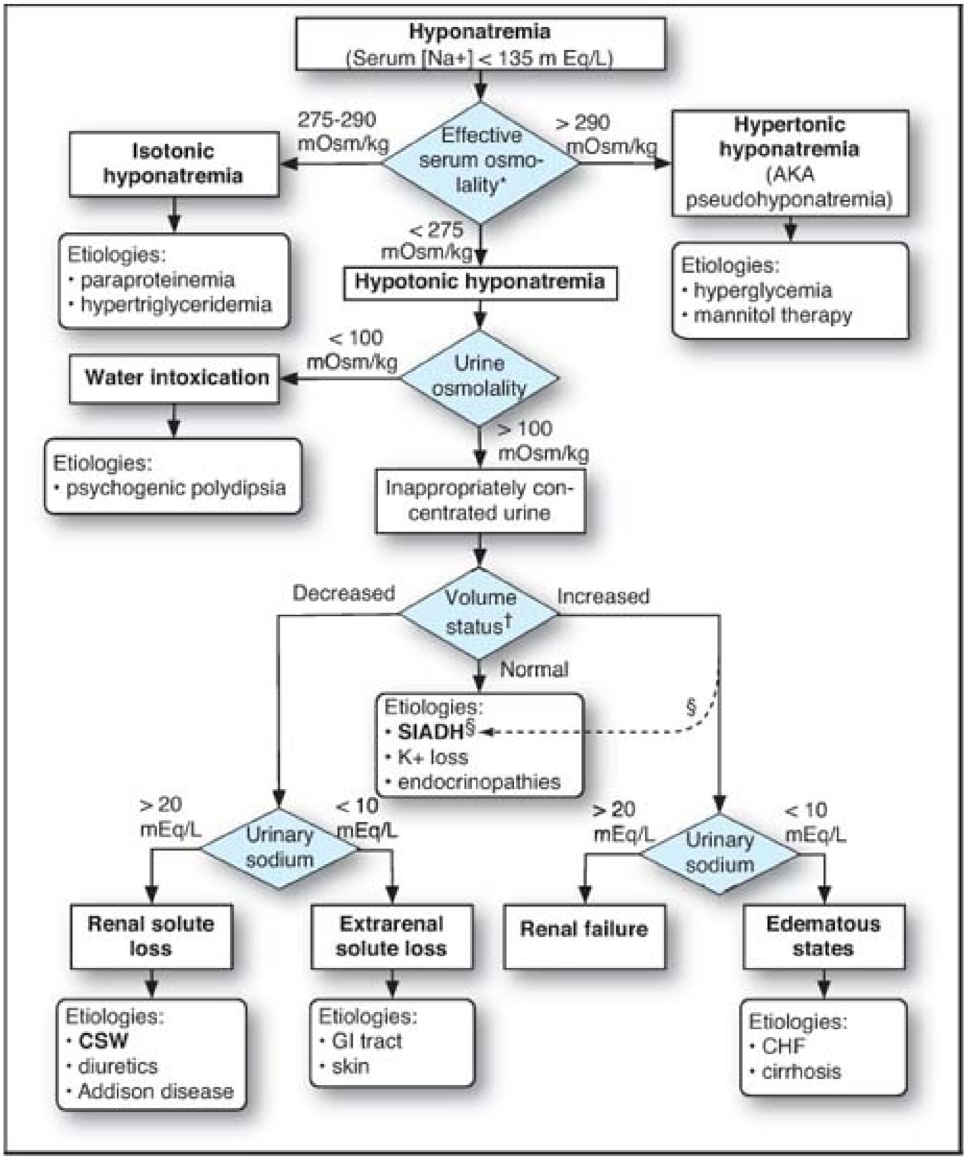

Figure 2-1 Evaluation of the etiology of hyponatremia
(adapted from Powers C, Friedman A H: Diagnosis and management of hyponatremia in neurosurgical patients. **Contemp Neurosurg** 29 (20): 1-5, 2007)

* effective serum osmolality = measured osmolality - [BUN]/2.8 (*see Eq 2-1*)

† volume status is usually assessed clinically, but this may be insensitive to volume depletion (*see text*)

§ SIADH may be associated with euvolemia or hypervolemia

$$\boxed{\text{effective serum osmolality} = \text{measured osmolality} - \frac{[\text{BUN}]\ (\text{mg/dl})}{2.8}} \qquad \textbf{Eq 2-1}$$

Work-up requires assessment of:

1. **serum sodium**: must be < 135 mEq/L to qualify as hyponatremia

2. ***effective*** **serum osmolality** (AKA tonicity): the definition is shown in *Eq 2-1*, and should be used when the blood urea nitrogen **(BUN)** level is elevated (for a normal [BUN] of 7-18 mg/dl, just subtract 5 from the measured osmolality). Values **< 275 mOsm/kg** indicate hypotonic hyponatremia
3. **urine osmolality**: values > 100 mOsm/kg are inappropriately high if serum tonicity is < 275 mOsm/kg
4. **volume status**: differentiates SIADH from CSW
   A. clinical assessment: better for hypervolemia (edema, upward trend in patient weights) but is insensitive in identifying extracellular fluid depletion as an etiology of hyponatremia[6] (look for dry mucous membranes, loss of skin turgor, orthostatic hypotension)
   B. **normal saline infusion test** used in uncertain cases. If base-line urine osmolality is < 500 mOsm/kg, it is usually safe to infuse 2 L of 0.9% saline over 24-48 hours. Correction of the hyponatremia suggests extracellular fluid volume depletion was the cause
   C. central venous pressure **(CVP)** may be used: CVP < 5-6 cm H_2O suggests hypovolemia in patients with normal cardiac function[3, 5]
5. check **urinary [Na^+]** if volume status is high or low
6. determine duration of hyponatremia:
   A. duration documented as < 48 hours is considered acute
   B. hyponatremia of > 48 hours duration or of unknown duration is chronic
   C. hyponatremia that occurs outside the hospital is usually chronic and asymptomatic except in marathoners and MDMA ("ecstasy") drug users

Table 2-2 Etiologies of SIAD*

Malignant tumors:
1. especially bronchogenic small-cell Ca 2. tumors of GI or GU tract 3. lymphomas 4. Ewing's sarcome
CNS disorders
1. infection: A. encephalitis B. meningitis: especially in peds C. TB meningitis D. AIDS E. brain abscess 2. head trauma: 4.6% prevalence

3. increased ICP: hydrocephalus, SDH… 4. SAH 5. brain tumors 6. cavernous sinus thrombosis 7. ★ post craniotomy, especially following surgery for pituitary tumors, craniopharyngiomas, hypothalamic tumors 8. MS 9. Guillain-Barré 10. Shy-Drager 11. delerium tremens (DTs)
Pulmonary disorders
1. infection: pneumonia (bacterial & viral), abscess, TB, aspergillosis 2. asthma 3. respiratory failure associated with positive pressure respiration
Drugs
1. drugs that release ADH or potentiate it A. chlorpropramide (Diabinese®): increasies renal sensitivity to ADH B. carbamazepine (Tegretol®), even more common with oxcarbazepine C. HCTZ (*see page 18*) D. SSRIs, TCAs E. clofibrate F. vincristine G. antipsychotics H. NSAIDs I. MDMA (“ecstasy”) 2. ADH analogues A. DDAVP B. oxytocin: ADH cross activity, may also be contaminated with ADH
Endocrine disturbances
1. adrenal insufficiency 2. hypothyroidism
Miscellaneous
1. anemia 2. stress, severe pain, nausea or hypotension (all can stimulate ADH release), postoperative state 3. acute intermittent porphyria **(AIP)**

* *excerpted and modified*[1, 7]

Symptoms

Due to slow compensatory mechanisms in the brain, a gradual decline in serum sodium is better tolerated than a rapid drop. Symptoms of mild ([Na] < 130 mEq/L) or gradual hyponatremia include: anorexia, headache, difficulty concentrating, irritability, dysgeusia and muscle weakness. Severe hyponatremia (< 125 mEq/L) or a rapid drop (> 0.5 mEq/hr) can cause neuromuscular excitability, cerebral edema, muscle twitching and cramps, nausea/vomiting, confusion, seizures, respiratory arrest and possibly permanent neurologic injury, coma or death.

SYNDROME OF INAPPROPRIATE ANTIDIURESIS (SIAD)

This term covers excess water retention in the face of hyponatremia, including cases due to inappropriate ADH secretion (SIADH, *see below*) as well as others without increased circulating levels of ADH (e.g. heightened response to ADH, certain drugs…). A partial list of etiologies is shown in *Table 2-2* (see references[1, 7] for details).

The diagnostic criteria of SIAD is shown in *Table 2-3*. It is critical to <u>measure serum osmolality</u> to rule-out pseudohyponatremia (*see page 7*) an artifact of indirect lab techniques.

Table 2-3 Diagnostic criteria for SIAD[1]

Essential features
• decreased effective serum osmolality* (< 275 mOsm/kg of water)
• simulatneous urine osmolality > 100 mOsm/kg of water
• clinical euvolemia A. no clinical signs of extracellular **(EC)** volume depletion (orthostatic hypotension, tachycardia, decreased skin turgor, dry mucous membranes…) B. no clinical signs of excess EC volume (edema, ascites…)
• urinary [Na] > 40 mEq/L with normal dietary Na intake
• normal thyroid and adrenal function
• no recent diuretic use
Supplemental features
• plasma [uric acid] < 4 mg/dl
• [BUN] < 10 mg/dl
• fractional Na excretion > 1%; fractional urea excretion > 55%
• NS infusion test: failure to correct hyponatremia with IV infusion of 2 L 0.9% saline over 24-48 hrs†
• correction of hyponatremia with fluid restriction
• abnormal result on water load test‡: A. < 80% excretion of 20 ml of water/kg body weight over 5 hours, or B. inadequate urinary dilution (< 100 mOsm/kg of water)
• elevated plasma [ADH]‡ with hyponatremia and euvolemia

* effective osmolality (AKA tonicity) = (measured osmolality) – [BUN]/2.8 with [BUN] measured in mg/dl

† this test is used n uncertain cases (corrects volume depletion), and is usually safe when baseline urine osmolality is < 500 mOsm/L

‡ water load test & [ADH] levels are rarely recommended (*see text* for details)

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH)

Key concepts:

> • definition: release of ADH in the absence of physiologic (osmotic) stimuli
> • results in hyponatremia with hypervolemia (occasionally with euvolemia)

with inappropriately high urine osmolality (> 100 mOsm/L)
- may be seen with certain malignancies and many intracranial abnormalities
- critical to distinguish from cerebral salt wasting which produces hypovolemia
- treatment: (initial guidelines in brief, *see page 11* for details)
  - avoid rapid correction or overcorrection to reduce risk of osmotic demyelination (*see page 11*). Check serum $[Na^+]$ q 2-4 hours and do not exceed 1 mEq/L per hour, or 8 mEq/L in 24 hrs or 18 mEq/L in 48 hrs
  - severe ($[Na^+]$ < 125 mEq/L of < 48 hrs duration or with severe symptoms (coma, Sz): start 3% saline at 1-2 ml/kg body weight/hr + furosemide 20 mg IV qd
  - severe ($[Na^+]$ < 125 mEq/L of duration > 48 hours or unknown without severe symptoms: normal saline infusion @ 100 ml/hr + furosemide 20 mg IV qd
  - chronic or unknown duration and asymptomatic: fluid restriction (*see Table 2-4*) with dietary salt and protein, and, if necessary, adjuvant drugs (demeclocycline, conivaptan…)

SIADH, AKA Schwartz-Bartter syndrome, was first described with bronchogenic cancer which is one cause of SIAD. SIADH is the release of antidiuretic hormone **(ADH)** (AKA arginine vasopressin **(AVP) -** *see page 111*) in the absence of physiologic (osmotic) stimuli. Result: elevated urine osmolality, and expansion of the extracellular fluid volume leading to a dilutional hyponatremia which can produce fluid overload (hypervolemia), but SIADH may also occur with euvolemia. For unclear reasons, edema does not occur.

The hyponatremia of SIADH must be differentiated from that due to cerebral salt wasting **(CSW)** (*see below*) due to differences in treatment recommendations.

Etiologies: *see Table 2-2*.

Diagnosis of SIADH

In general, 3 diagnostic criteria are: hyponatremia, inappropriately concentrated urine, and no evidence of renal or adrenal dysfunction. In more detail:

1. low serum sodium (hyponatremia): usually < 134 mEq/L
2. low effective serum osmolality: < 275 mOsm/L
3. high urinary sodium[A] (salt wasting): at least > 18 mEq/L, often 50-150

4. high ratio of urine:serum osmolality: often 1.5-2.5:1, but may be 1:1
5. normal renal function (check BUN & creatinine): BUN commonly < 10
6. normal adrenal function (no hypotension, no hyperkalemia)
7. no hypothyroidism
8. no signs of dehydration or overhydration (in many patients with acute brain disease, there is significant hypovolemia often due to CSW (*see below*) and as this is a stimulus for ADH secretion, the ADH release may be "appropriate"[8]). In uncertain cases, the NS infusion test may be used (*see page 9*)

A. there has not been an adequate explanation of the high urinary sodium in SIADH

If further testing is required, the following are options, but are rarely recommended:

1. measure serum or urinary levels of ADH. Rarely indicated since urine osmolality > 100 mOsm/kg is usually sufficient to indicate excessive ADH[1]. ADH is normally undetectable in etiologies of hyponatremia other than SIADH
2. **water-load test**: considered to be the definitive test[9]. The patient is asked to consume a water load of 20 ml/kg up to 1500 ml. In the absence of adrenal or renal insufficiency, the failure to excrete 65% of the water load in 4 hrs or 80% in 5 hrs indicates SIAD. ✖ CONTRAINDICATIONS: this test is dangerous if the starting serum [Na^+] is ≤ 124 mEq/L or if the patient has symptoms of hyponatremia

Symptoms of SIADH

Symptoms are those of hyponatremia (*see page 9*) and possibly fluid overload. If mild, or if descent of [Na^+] is gradual, it may be tolerated. [Na^+] < 120-125 mEq/L is almost always symptomatic. These patients often have a paradoxical (inappropriate) thirst.

Treatment of hyponatremia with SIADH

Management is based on the severity and duration of hyponatremia, and the presence of symptoms. Two caveats:

1. ✖ be sure that hyponatremia is not due to CSW (*see below*) before

restricting fluids

2. avoid too rapid correction or correction to normal or supranormal (overcorrection) sodium to reduce the risk of osmotic demyelination syndrome (*see below*)

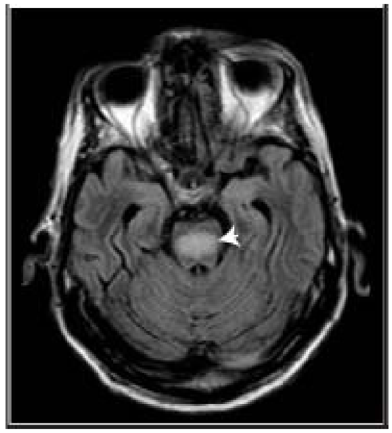

Figure 2-2 Central pontine myelinolysis (arrowhead). Axial FLAIR MRI

Osmotic demyelination syndrome: A complication associated with some cases of treatment for hyponatremia. While excessively slow correction of acute hyponatremia is associated with increased morbidity and mortality[10], some cases of inordinately rapid treatment have been associated with osmotic demyelination syndrome (which includes **central pontine myelinolysis (CPM)** a rare disorder of pontine white matter[11] (*see Figure 2-2*) and extrapontine myelinolysis (*see Figure 2-3*), as well as other areas of cerebral white matter). First described in alcoholics[12], producing insidious flaccid quadriplegia, mental status changes, and cranial nerve abnormalities with a pseudobulbar palsy appearance. In one review[13], no patient developed CPM when treated slowly as outlined below. And yet, the rate of correction correlates poorly with CPM; it may be that the magnitude is another critical variable[14]. Features common to patients who develop CPM are[13]:

- delay in the diagnosis of hyponatremia with resultant respiratory arrest or seizure with probable hypoxemic event
- rapid correction to normo- or hypernatremia (> 135 mEq/L) within 48 hours of initiating therapy
- increase of serum sodium by > 25 mEq/L within 48 hours of initiation of therapy
- over-correcting serum sodium in patients with hepatic encephalopathy

- NB: many patients developing CPM were victims of chronic debilitating disease, malnourishment, or alcoholism and never had hyponatremia. Many had an episode of hypoxia/anoxia[15]
- presence of hyponatremia > 24 hrs prior to treatment[14]

Treatment of underlying cause

The only definitive treatment

- if caused by anemia: usually responds to transfusion
- if caused by malignancy, may respond to antineoplastic therapy
- most drug related cases respond rapidly to discontinuation of the offending drug

Figure 2-3 Osmotic demyelination of pons (black arrowhead) & thalamus (white arrowhead). Coronal T2WI MRI

Treatment algorithms

Figure 2-4 depicts an algorithm for selecting the correct SIADH treatment protocol.

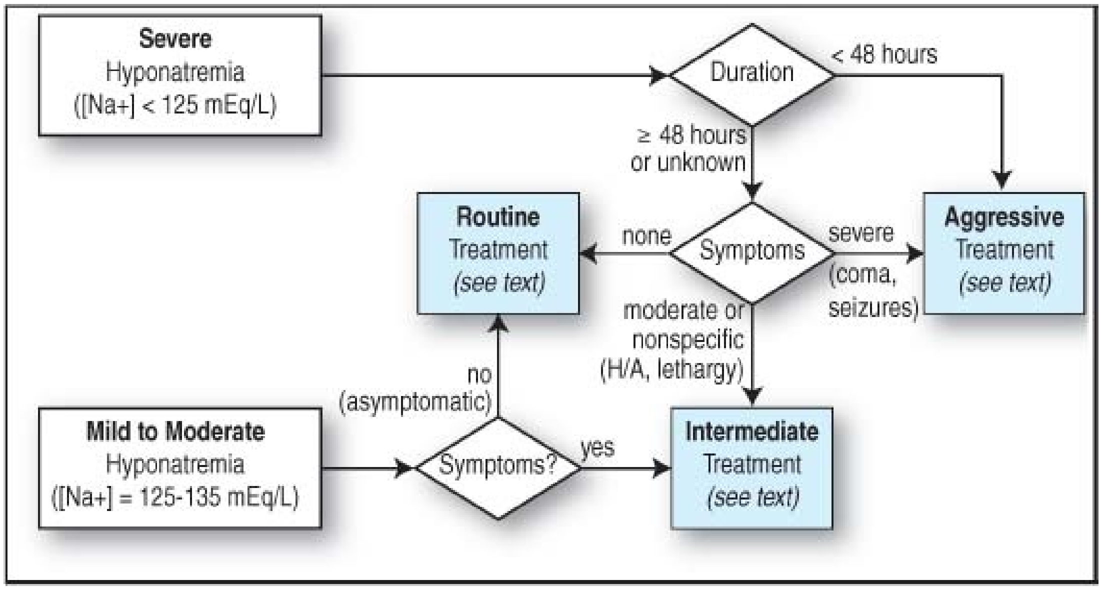

Figure 2-4 Treatment protocol selection for hyponatremia in SIADH

Aggressive treatment protocol

Indications (also refer to *Figure 2-4*):

1. severe hyponatremia (serum $[Na^+]$ < 125 mEq/L)
2. AND either
   A. duration known to be < 48 hours
   B. or severe symptoms (coma, seizures)

Treatment

1. transfer patient to ICU
2. medications
   A. 3% saline: start infusion 1-2 ml/kg body weight per hour[A]
   B. and furosemide[B] (Lasix®) 20 mg IV q d
3. check serum $[Na^+]$ every 2-3 hours and adjust infusion rate of 3% saline
   A. goal: raise serum sodium by 1-2 mEq/L/hr[16] (use lower end of range for hyponatremia > 48 hours duration or unknown duration)
   B. limits: do not exceed 8-10 mEq/L in 24 hrs and 18-25 mEq/L in 48 hrs[1] (use lower end of these ranges for hyponatremia > 48 hours duration or unknown duration)
4. measure K^+ lost in urine and replace accordingly
5. if symptoms of osmotic demyelination occur (early symptoms are lethargy and affective changes, usually after initial improvement): deficits may

improve by stopping treatment and modestly relowering the serum sodium e.g. with DDAVP[17, 18]

A. infusion rate may be doubled to 2-4 ml/kg/hr for limited periods in patients with coma or seizures[1]

B. furosemide accelerates the increase in [Na^+] and prevents volume overload with subsequent increase in atrial natriuretic factor and resultant urinary dumping of the extra Na^+ being administered

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Intermediate treatment protocol

Indications (also refer to *Figure 2-4*):

1. symptomatic nonsevere hyponatremia (serum [Na^+] = 125-135 mEq/L), or
2. severe hyponatremia (serum [Na^+] < 125 mEq/L), AND
   A. duration > 48 hours or unknown AND
   B. only moderate symptoms or nonspecific symptoms (e.g. H/A, or lethargy)

Treatment

1. medications
   A. 0.9% saline (normal saline) infusion
   B. and furosemide (Lasix®) 20 mg IV q d
   C. consider conivaptan (*see below*) for refractory cases
2. check serum [Na^+] every 4 hours and adjust infusion rate of normal saline
3. goals: [Na^+] increase of 0.5-2 mEq/L/hr
4. limits: do not exceed 8-10 mEq/L in 24 hrs and 18-25 mEq/L in 48 hrs[1]

Routine treatment protocol and maintenance therapy

Indications (also refer to *Figure 2-4*):

1. asymptomatic nonsevere hyponatremia (serum [Na^+] = 125-135 mEq/L), or
2. severe hyponatremia (serum [Na^+] < 125 mEq/L) AND
   A. duration > 48 hours or unknown AND
   B. asymptomatic

Treatment

1. interventions

A. fluid restriction (*see Table 2-4* for adults, for peds: 1 $L/m^2/day$) while encouraging use of dietary salt and protein. Caution restricting fluids in hyponatremia following SAH (*see page 1043*)

B. for refractory cases, consider

1. **demeclocycline**: a tetracycline antibiotic that partially antagonizes the effects of ADH on the renal tubules[19-21]. Effects are variable, and nephrotoxicity may occur. ***Rx*** 300-600 mg PO BID
2. **conivaptan** (Vaprisol®): a nonpeptide antagonist of V_{1A} & V_2 vasopressin receptors. FDA approved for euvolemic and hypervolemic moderate-to-severe hyponatremia in hospitalized patients (NB: severe symptoms of seizures, coma, delerium… warrants aggressive treatment with hypertonic saline[1]). Use in the neuro-ICU has been described for treating elevated ICP when serum [Na] is not responding to traditional methods[22] (off-label use - use with caution). ***Rx*** loading dose 20 mg IV over 30 minutes, followed by infusions of 20 mg over 24 hours **x** 3 days. If serum $[Na^+]$ are not rising as desired, the infusion may be increased to the maximal dose of 40 mg over 24 hours. Use is approved for up to 4 days total. Caution re drug interactions
3. **lithium**: not very effective and many side effects. Not recommended

Table 2-4 Fluid restriction recommendations[1]

Solute ratio*	Recommended fluid intake
> 1	< 500 ml/d
1	500-700 ml/d
< 1	< 1 L/d

* *solute ratio defined as:*

$$\frac{\text{urinary [Na]} + \text{urinary [K]}}{\text{plasma [Na]}}$$

CEREBRAL SALT WASTING

Cerebral salt wasting (CSW): renal loss of sodium as a result of intracranial disease, producing hyponatremia and a decrease in extracellular fluid volume[9]. CAUTION: patients with aneurysmal SAH may have CSW with hyponatremia which mimics SIADH, however there is usually also hypovolemia

in CSW. In this setting, fluid restriction may exacerbate vasospasm induced ischemia[9, 23-25].

The mechanism whereby the kidneys fail to conserve sodium in CSW is not known, and may be either a result of an as yet unidentified natriuretic factor or direct neural control mechanisms (see *Hyponatremia following SAH*, page 1043).

Laboratory tests (serum and urinary electrolytes and osmolalities) may be identical with SIADH and CSW[26]. Further-more, hypovolemia in CSW may stimulate ADH release. To differentiate: CVP, PCWP, and plasma volume (a nuclear medicine study) are low in hypovolemia (i.e. CSW). *Table 2-5* compares some features of CSW and SIADH, the two most important differences being extracellular volume and salt balance. An elevated serum [K^+] with hyponatremia is incompatible with the diagnosis of SIADH.

Table 2-5 Comparison of CSW and SIADH[9]*

Parameter	CSW	SIADH
★ Plasma volume	↓ (< 35 ml/kg)	↑ or WNL
★ Salt balance	negative	variable
Signs & symptoms of dehydration	present	absent
Weight	↓	↑ or no Δ
PCWP	↓ (< 8 mm Hg)	↑ or WNL
CVP	↓ (< 6 mm Hg)	↑ or WNL
Orthostatic hypotension	+	±
Hematocrit	↑	↓ or no Δ
Serum osmolality	↑ or WNL[†]	↓
Ratio of serum BUN]:[creatinine]	↑	WNL
Serum [protein]	↑	WNL
Urinary [Na^+]	↑↑	↑
Serum [K^+]	↑ or no Δ	↓ or no Δ
Serum [uric acid]	WNL	↓

* abbreviations: ↓ = decreased, ↑ = increased, ↑↑ = significantly increased, WNL = within normal limits, no Δ = no change, [] = concentration, + = present, ± = may or may not be present

† in reality, serum osmolality is usually ↓ in CSW

Treatment of CSW

Goals: volume replacement and positive salt balance.

Hydrate patient with 0.9% NS at 100-125 ml/hr. Do not give furosemide. For severe cases, 3% saline at 25-50 cc/hr is occasionally required. Salt may also be simultaneously replaced orally. Blood products may be needed if anemia is present.

Rapid correction of hyponatremia may be associated with osmotic demyelination (*see page 11*) and care should be taken to avoid overcorrection, as with SIADH (*see page 11*).

Fludrocortisone acetate acts directly on the renal tubule to increase sodium absorption. Benefits of giving 0.2 mg IV or PO q d in CSW have been reported[27], but significant complications of pulmonary edema, hypokalemia and HTN may occur.

Urea: an alternative treatment using urea may be applicable to the hyponatremia of either SIADH *or* CSW, and therefore may be used before the cause has been ascertained: urea (Ureaphil®) 0.5 grams/kg (dissolve 40 gm in 100-150 ml NS) IV over 30-60 mins q 8 hrs[28]. Use NS + 20 mEq KCl/L at 2 ml/kg/hr as the main IV until the hyponatremia is corrected (unlike mannitol, urea does not increase ADH secretion). They supplemented with colloids (viz. 250 ml of 5% albumin IV q 8-12 hrs **x** 72 hrs).

HYPERNATREMIA

Definition: serum sodium > 150 mEq/L. In neurosurgical patients, this is most often seen in the setting of diabetes insipidus **(DI)** (*see below*).

Since normal total body water **(TBW)** is ≈ 60% of the patient's normal body weight, the patient's current TBW may be estimated by *Eq 2-2*.

$$TBW_{current} = \frac{[Na^+]_{normal} \times TBW_{normal}}{[Na^+]_{current}} = \frac{140\ mEq/L \times 0.6 \times \text{usual body wt (kg)}}{[Na^+]_{current}} \quad \text{Eq 2-2}$$

The free water deficit to be replaced is given by *Eq 2-3*. Correction must be made slowly to avoid exacerbating cerebral edema. One half the water deficit is replaced over 24 hours, and the remainder is given over 1-2 additional days. Judicious replacement of deficient ADH in cases of true DI must also be made (*see below*).

$$\text{free water deficit} = 0.6 \times \text{usual body wt (kg)} - TBW_{current}$$

$$= \frac{[Na^+]_{current} - 140\text{ mEq/L}}{[Na^+]_{current}} \times 0.6 \times \text{usual body wt (kg)}$$

Eq 2-3

DIABETES INSIPIDUS

Key concepts:

- due to low levels of ADH (or, rarely, renal insensitivity to ADH)
- high output of dilute urine (< 200 mOsmol/L or SG < 1.003) with normal or high serum osmolality and high serum sodium
- often accompanied by craving for water, especially ice-water
- danger of severe dehydration if not managed carefully

Diabetes insipidus **(DI)** is due to insufficient ADH, and results in the excessive renal loss of water and electrolytes. DI may be produced by two different etiologies:

- central or neurogenic DI: subnormal levels of ADH caused by hypothalamic-pituitary axis dysfunction. This is the type most often seen by neurosurgeons
- "**nephrogenic DI**": due to relative resistance of the kidney to normal or supra-normal levels of ADH. Seen with some drugs (*see below*)

Etiologies of DI[29]:

1. (neurogenic) diabetes insipidus
   - A. familial (autosomal dominant)
   - B. idiopathic
   - C. posttraumatic (brain injury, including surgery)
   - D. tumor: craniopharyngioma, metastasis, lymphoma…
   - E. granuloma: neurosarcoidosis, histiocytosis
   - F. infectious: meningitis, encephalitis
   - G. autoimmune
   - H. vascular: aneurysm, Sheehan's syndrome (rarely causes DI)
2. nephrogenic diabetes insipidus
   - A. familial (X-linked recessive)
   - B. hypokalemia
   - C. hypercalcemia

D. Sjögren's syndrome
E. drugs: lithium, demeclocycline, colchicine…
F. chronic renal disease: pyelonephritis, amyloidosis, sickle cell disease, polycystic kidney disease, sarcoidosis

Central DI

85% of ADH secretory capacity must be lost before clinical DI ensues. Characteristic features: high urine output (polyuria) with low urine osmolality, and (in the conscious patient) craving for water (polydipsia), especially ice-water.

Differential diagnosis of DI:

1. (neurogenic) diabetes insipidus (true DI)
2. nephrogenic diabetes insipidus
3. psychogenic
   A. idiopathic: from resetting of the osmostat
   B. psychogenic polydipsia (excess free water intake)
4. osmotic diuresis: e.g. following mannitol, or with renal glucose spilling
5. diuretic use: furosemide, hydrochlorothiazide…

Central DI may be seen in the following situations:

1. following transsphenoidal surgery or removal of craniopharyngioma: (usually transient, therefore avoid long-acting agents until it can be determined if long-term replacement is required). Injury to the posterior pituitary or stalk usually causes one of three patterns of DI[30]:
   A. transient DI: supra-normal urine output **(UO)** and polydipsia which typically normalizes ≈ 12-36 hrs post-op
   B. "prolonged" DI: UO stays supra-normal for prolonged period (may be months) or even permanently: only about one third of these patients will not return to near-normal at one year post-op
   C. "**triphasic response**": least common
      - phase 1: injury to pituitary reduces ADH levels for 4-5 days → DI (polyuria/polydipsia)
      - phase 2: cell death liberates ADH for the next 4-5 days → transient normalization or even SIADH-like water retention (✖ NB: there is a danger of inadvertently continuing vasopressin therapy beyond the initial DI phase into this phase causing significant hemodilution)

- phase 3: reduced or absent ADH secretion → either transient DI (as in "A" above) or a "prolonged" DI (as in "B" above)

2. central herniation: shearing of pituitary stalk may occur (*see page 285*)
3. brain death: hypothalamic production of ADH ceases
4. with certain tumors:
   A. pituitary adenomas: DI is rare even with very large macroadenomas. DI may occur with pituitary apoplexy (*see page 635*)
   B. craniopharyngioma: DI usually only occurs postoperatively since damage to pituitary or lower stalk does not prevent production and release of ADH by hypothalamic nuclei
   C. suprasellar germ cell tumors
   D. rarely with a colloid cyst
   E. hypothalamic tumors: eosinophilic granuloma
5. mass lesions pressing on hypothalamus: e.g. a-comm aneurysm
6. following head injury: primarily with basal (clival) skull fractures (*see page 889*)
7. with encephalitis or meningitis
8. drug induced:
   A. ethanol and phenytoin can inhibit ADH release
   B. exogenous steroids may seem to "bring out" DI because they may correct adrenal insufficiency (see *Diagnosis* below) and they inhibit ADH release
9. granulomatous diseases
   A. Wegener's granulomatosis: a vasculitis (*see page 78*)
   B. neurosarcoidosis involving the hypothalamus (*see page 71*)
10. inflammatory: autoimmune hypophysitis[31] (*see page 1217*) or lymphocytic infundibuloneurohypophysitis[32] (distinct conditions)

Diagnosis

The following are usually adequate to make the diagnosis of DI, especially in the appropriate clinical setting:

1. dilute urine:
   A. **urine osmolality < 200** mOsm/L (usually 50-150)[A] or **specific gravity (SG) < 1.003** (may be 1.001 to 1.005)
   B. or the inability to concentrate urine to > 300 mOsm/L in the presence of clinical dehydration

C. NB: large doses of mannitol as may be used in head trauma can mask this by producing a more concentrated urine
2. urine output **(UO)** > 250 cc/hr (peds: > 3 cc/kg/hr)
3. normal or above-normal serum sodium
4. normal adrenal function: DI cannot occur in primary adrenal insufficiency because a minimum of mineralocorticoid activity is needed for the kidney to make free water, ∴ steroids may reveal latent DI by correcting adrenal insufficiency

---

A. normally, urine osmolality averages between 500-800 mOsm/L (extreme range: 50-1400)

In uncertain cases, plot urine and simultaneous serum osmolality on the graph in *Figure 2-5*:

1. low serum osmolality: the patient has polydipsia
2. if the point falls in the "normal" range, a supervised water deprivation test is needed to determine if the patient can concentrate their urine with dehydration (caution: *see below*)
3. high serum osmolality: diagnosis of DI is established, and further testing is not needed (except to differentiate central from nephrogenic DI, if desired)
   • to differentiate central from nephrogenic DI, give aqueous Pitressin® 5 U SQ: in central DI the urine osmolality should double within 1-2 hours
4. plotting more than one data point may help as some patients tend to "vacillate" around the border zones

Water deprivation test

If still unclear, the diagnosis of DI is confirmed by a water deprivation test (✖ CAUTION: perform only under close supervision as rapid and potentially fatal dehydration may ensue in DI). This test is rarely necessary if serum osmolality > 298 mOsm/L[A]. Stop IVs and make the patient NPO; check urine osmolality q hr.

1. continue the test until one of the following occurs:
   A. normal response occurs: urine output decreases, and urine osmolality rises to 600-850 mOsm/L
   B. 6-8 hours lapse
   C. urine osmolality plateaus (i.e. changes < 30 mOsm in 3 consecutive

hours)

D. patient loses 3% of body weight

2. if patient fails to demonstrate the normal response, then:

A. give exogenous ADH (5 U aqueous Pitressin® SQ), which normally increases urine osmolality to > 300 mOsm/L

B. check urine osmolality 30 and 60 minutes later

C. compare highest urine osmolality after Pitressin® to the osmolality just before Pitressin® according to *Table 2-6*

A. in compensated DI serum osmolality is more likely to be lower and to overlap with normals[33]

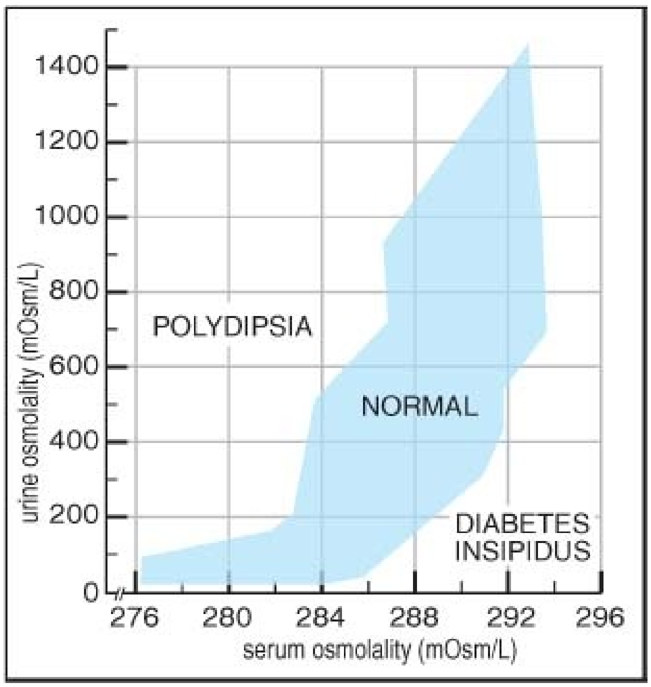

Figure 2-5 Interpretation of simultaneous serum vs. urine osmolality
(Provided by Arnold M. Moses, M.D., used with permission)

Table 2-6 Highest urinary osmolality after Pitressin in water deprivation test

Δ in urinary Osm	Interpretation
< 5% increase	normal
6-67% increase	partial ADH deficiency
> 67% increase	severe ADH deficiency

TREATMENT OF DI

See *Table 2-7* and *Table 2-8* for dosing forms and duration of action of vasopressin analogues.

Pitressin® is aqueous solution of 8-arginine vasopressin and should be used with caution in patients with vascular disease (especially coronary arteries). ✖ Caution in pre-scribing: sometime pitocin is confused with pitressin because of similarities of the name.

DDAVP (1-deamino-8-D-arginine vasopressin) AKA **desmopressin**. More potent and longer acting than vasopressin.

Table 2-7 Available preparations of vasopressin analogues

Generic name	Trade name	Route	Concentration	Availability	Manufacturer
desmopressin	DDAVP®	SQ, IM, IV	4 mcg/ml	1 & 10 ml	Aventis
desmopressin	DDAVP® Nasal Spray	nasal spray	100 mcg/ml, each spray delivers 10 mcg	50 doses per bottle	Aventis
desmopressin	DDAVP® Tablets	PO		0.1 & 0.2 mg	Aventis
arginine vaso-pressin	aqueous Pitressin®	SQ, IM	20 U/ml (50 mcg/ml)	0.5 and 1 ml	Parke-Davis
posterior pituitary powder in oil	Pitressin tannate in oil	IM (poor ab-sorption)	5 U/ml	1 ml	Parke-Davis

In <u>conscious</u> ambulatory patient

If DI is mild, and natural thirst mechanism is intact, instruct patient to drink <u>only</u> when thirsty and they usually "keep up" with losses and will not become overhydrated. If severe, patient may not be able to continue adequate intake of fluid (and constant trips to bathroom), in this case administer either:

1. desmopressin (DDAVP®)
   A. PO: 0.1 mg PO BID, adjust up or down PRN urine output (typical dosage range: 0.1-0.;8 mg/d in divided doses)
   B. nasal spray: 2.5 mcg (0.025 ml) by nasal insufflation BID, titrate up to 20 mcg BID as needed (the nasal *spray* may be used for doses that are multiples of 10 mcg)

OR

2. ADH enhancing medications (works primarily in chronic partial ADH deficiency. Will not work in total absence of ADH)
   A. clofibrate (Atromid S®) 500 mg PO QID
   B. chlorpropramide: increases renal sensitivity to ADH
   C. hydrochlorothiazide: thiazide diuretics may act by depleting Na^+

which increases reabsorption in proximal tubules and shifting fluid away from distal tubules which is where ADH works. ***Rx***: e.g. Dyazide® 1 PO q d (may increase up to 2 per day PRN)

Table 2-8 Mean time of hypertonic urine* (relative to plasma)†

Generic name	Route	Dose	Mean duration of action‡
desmopressin	SQ, IM, IV	0.5 mcg	8 hrs
desmopressin§	SQ, IM, IV	1.0 mcg	12 hrs
desmopressin	SQ, IM, IV	2.0 mcg	16 hrs
desmopressin	SQ, IM, IV	4.0 mcg	20 hrs
desmopressin	intranasal	10 mcg (0.1 ml)	12 hrs
desmopressin	intranasal	15 mcg (0.15 ml)	16 hrs
desmopressin	intranasal	20 mcg (0.2 ml)	20 hrs
arginine vasopressin	SQ, IM	5 U (12.5 mcg)	4 hrs (range: 4-8)
posterior pituitary powder in oil	IM	5 U	48-72 hrs

* provided by Arnold M. Moses, M.D., used with permission

† onset of antidiuretic action of these preparations is 30-45 minutes following administration (except pituitary powder in oil which takes 2-4 hrs to start working)

‡ times may vary from patient to patient, but are usually consistent in any individual

§ Note: 1 mcg BID of desmopressin is as effective as 4 mcg q d, but would obviously be less expensive

In <u>conscious</u> ambulatory patient with impaired thirst mechanisms

If thirst mechanisms are <u>not</u> intact in conscious ambulatory patient, they run the risk of dehydration or fluid overload. For these patients:

1. have patient follow UO and daily weights, balance fluid intake and output using antidiuretic medication as needed to keep UO reasonable
2. check serial labs (approximately q weekly) including serum sodium, BUN

In non-ambulatory, comatose/stuporous, or brain-dead patient

(also see *Management after brain death for organ donation*, page 294)

1. follow I's & O's q 1 hr, with urine specific gravity **(SG)** q 4 hrs and whenever urine output **(UO)** > 250 ml/hr

2. labs: serum electrolytes with osmolality q 6 hrs
3. IV fluid management:
   BASE IV: D5 1/2 NS + 20 mEq KCl/L at appropriate rate (75-100 ml/hr)
   PLUS: replace UO above base IV rate ml for ml with 1/2 NS

   NB: for post-op patients, if the patient received significant intraoperative fluids, then they may have an appropriate post-op diuresis, in this case use 1/2 NS to replace only ≈ 2/3 of UO that exceeds the basal IV rate
4. if unable to keep up with fluid loss with IV (or NG) replacement (usually with UO > 300 ml/hr), then EITHER
   - 5 U arginine vasopressin (aqueous Pitressin®) IVP/IM/SQ q 4-6 hrs (avoid tannate oil suspension due to erratic absorption and variable duration)
   - or vasopressin IV drip: start at 0.2 U/min & titrate (max: 0.9 U/min)
   - or desmopressin injection SQ/IV titrated to UO, usual adult dose: 0.5-1 ml (2-4 mcg) daily in 2 divided doses

2.1.2. Serum osmolality

Clinical significance of various serum osmolarity values is shown in *Table 2-9*.

Table 2-9 Clinical correlates of serum osmolality

Value (mOsm/L)	Comment
282-295	normal
< 240 or > 321	panic values
> 320	risk of renal failure
> 384	produces stupor
> 400	risk of generalized seizures
> 420	usually fatal

Serum osmolality may be estimated using using *Eq 2-4* (with [Na^+] in mEq/L or mmol/L, and glucose and BUN in mg/dL).

$$\text{Osmolality (mOsm/L)} = 2 \times \{[Na^+] + [K^+]\} + \frac{[BUN]}{2.8} + \frac{[glucose]}{18} \qquad \textbf{Eq 2-4}$$

NB: terms in square brackets [] represent the serum concentrations (in mEq/L for electrolytes).

2.2. Blood pressure management

2.2.1. Hypertension

PARENTERAL AGENTS

Table 2-10 shows some parenteral agents for acute control of hypertension grouped based on their effect on ICP[34, 35].

Table 2-10 Effect of antihypertensives on ICP

Agents that may raise ICP (mostly vasodilators)	Agents that do not raise ICP
nitroglycerin (NTG)	trimethaphan (Arfonad®)
nitroprusside (NTP) (Nipride®)	methyldopa (Aldomet®)
	labetalol (Normodyne®…)
	nicardipine (Cardene®)

★ nicardipine (Cardene®) DRUG INFO

Calcium channel blocker **(CCB)** that may be given IV. Unlike NTP, does not require arterial line, does not raise ICP, and no cyanide toxicity. Does not reduce heart rate, but may be used in conjunction with e.g. labetalol or esmolol if that is desired. **SIDE EFFECTS:** H/A 15%, nausea 5%, hypotension 5%, reflex tachycardia 3.5%.

Rx start at 5 mg/hr IV (off label: 10 mg/hr may be used in situations where urgent reduction is needed). Increase by 2.5 mg/hr every 5-15 minutes up to a maximum of 15 mg/hr. Decrease to 3 mg/hr once control is achieved. ✖ Ampules contain 25 mg and must be diluted before administration.

✖ nitroprusside (NTP) (Nipride®) DRUG INFO

Use is diminishing because of side effects and effect on ICP. Raises ICP in patients with intracranial mass lesions[36] due to direct vasodilatation, arterial > venous (small coronaries > large). May preferentially dilate peripheral vessels before cerebral vessels, thus producing a "cerebral steal" phenomenon. Acts in seconds, duration 3-5 min.

SIDE EFFECTS: thiocyanate and cyanide toxicity (may cause neurologic deterioration[37] or hypotension) (follow thiocyanate levels if used > 24 hrs, at a rate ≥ 10 mcg/kg/min, or in renal failure; D/C if thiocyanate levels > 10 mg%), tachycardia, tachyphylaxis, hypotension which can extend an MI, "coronary steal". Avoid in pregnancy.

Rx IV drip 0.25-8 mcg/kg/min (ave. = 3). To reduce risk of cyanide toxicity, start at very low rate of 0.3 mcg/kg/min, and do not give maximum rate of 10 mcg/kg/min for more than 10 minutes. To prepare: put 50 mg in 500 ml D5W (can only be mixed in D5W; solution can be double concentrated to reduce fluid or glucose load) = 100 mcg/ml; cover bottle with foil (light sensitive).

nitroglycerin (NTG) DRUG INFO

Raises ICP (less than with nitroprusside due to preferential venous action[36]). Vasodilator, venous > arterial (large coronaries > small). Result: decreases LV filling pressure (pre-load). Does not cause "coronary steal" (cf nitroprusside).

Rx 10-20 mcg/min IV drip (increase by 5-10 mcg/min q 5-10 min). For angina pectoris: 0.4 mg SL q 5 min **x** 3 doses, check BP before each dose.

labetalol (Normodyne®, Trandate®) DRUG INFO

Blocks α_1 selective, ß non-selective (potency < propranolol). ICP reduces or no change[38]. Pulse rate: decreases or no change. Cardiac output does not change. Does not exacerbate coronary ischemia. May be used in controlled CHF, but not in overt CHF. Contraindicated in asthma. Renal failure: same dose. **SIDE EFFECTS:** fatigue, dizziness, orthostatic hypotension.

Intravenous (IV)

Onset 5 mins, peak 10 mins, duration 3-6 hrs.

Rx IV: patient supine; check BP q 5 min; give each dose slow IVP (over 2 min) q 10 minutes until desired BP achieved; dose sequence: 20, 40, 80, 80, then 80 mg (300 mg total). Once controlled, use ≈ same total dose IVP q 8 hrs.

Rx IV drip: add 40 ml (200 mg) to 160 ml of IVF (result: 1 mg/ml); run at 2 ml/min (2 mg/min) until desired BP (usual effective dose = 50-200 mg) or until 300 mg given; then titrate rate (bradycardia limits dose, increase slowly since effect takes 10-20 minutes).

Oral (PO)

Undergoes first pass liver degradation, therefore requires higher doses PO. PO onset: 2 hrs, peak: 4 hrs.

Rx PO: to convert IV → PO, start with 200 mg PO BID. To start with PO, give 100 mg BID, and increase 100 mg/dose q 2 day; max. = 2400 mg/day.

enalaprilat (Vasotec®) DRUG INFO

An angiotensin-converting enzyme **(ACE)** inhibitor. The active metabolite of the orally administered drug enalapril (*see below*). Acts within ≈ 15 mins of administration.

SIDE EFFECTS: hyperkalemia occurs in ≈ 1%. Do not use during pregnancy.

Rx IV: start with 1.25 mg slow IV over 5 mins, may increase up to 5 mg q 6 hrs PRN.

esmolol (Brevibloc®) DRUG INFO

Cardioselective short-acting beta blocker[39]. Being investigated for hypertensive emergencies. Metabolized by RBC esterase. Elimination half-life: 9 mins. Therapeutic response (> 20% decrease in heart rate, HR < 100, or conversion to sinus rhythm) in 72%. **SIDE EFFECTS:** dose related hypotension (in 20-50%), generally resolves within 30 mins of D/C. Bronchospasm less likely than other beta blockers. Avoid in CHF.

Rx 500 mcg/kg loading dose over 1 min, follow with 4 min infusion starting with 50 mcg/kg/min. Repeat loading dose and increment infusion rate by 50 mcg/kg/min q 5 mins. Rarely > 100 mcg/kg/min required. Doses > 200

mcg/kg/min add little.

fenoldopam (Corlopam®) DRUG INFO

Vasodilator. Onset of action < 5 minutes, duration 30 mins.

Rx IV infusion (no bolus doses): start with 0.1-0.3 mcg/kg/min, titrate by 0.1 mcg/kg/min q 15 min up to a maximum of 1.6 mcg/kg/min.

propranolol (Inderal®) DRUG INFO

Main use IV is to counteract tachycardia with vasodilators (usually doesn't lower BP acutely when used alone).

Rx IV: load with 1-10 mg slow IVP, follow with 3 mg/hr. PO: 80-640 mg q d in divided doses.

ORAL AGENTS

For less urgent control of HTN (exception: sublingual nifedipine (*see below*)).

clonidine (Catapres®) DRUG INFO

Acts on cardiovascular control receptors in medulla oblongata, inhibits sympathetic outflow. Less confusion than Aldomet, but still sedating. Tachycardia rare. Onset: < 30 min.

SIDE EFFECTS: fluid retention (which may reduce effectiveness, counter with diuretic), dry mouth, sedation (minimize by slow dose increments), constipation, decreased CO & HR (by increased vagal tone), rebound HTN if withdrawn rapidly (caution in unreliable patients; treatment for rebound HTN: clonidine and labetalol, *see page 20*). Rebound is less likely and less severe with clonidine patches (Catapres TTS®), applied once per week.

Rx Rapid control: 0.2 mg PO, then 0.1 mg PO q 1 hr, stop at 0.8 mg total or if orthostatic. Maintenance dose: 0.1 mg PO BID or TID, increase slowly to max. 2.4 mg/day (usual 0.2-0.8 mg/day).

propranolol (Inderal®) DRUG INFO

Beta blocker. Use in HTN: blunts reflex tachycardia from vasodilators.

SIDE EFFECTS: CHF, symptomatic bradycardia, bronchospasm (avoid in asthmatics), rapid withdrawal → reflex tachycardia → exacerbates myocardial ischemia in CAD.

Rx 40 mg PO BID (usually with diuretic), titrate up to 640 mg/day in 2-3 divided doses. Or, Inderal-LA, 80 mg PO q d. **SUPPLIED**: 10, 20 40, 60 & 80 mg scored tabs. Inderal-LA (long acting) 60, 80, 120 & 160 mg capsules.

nifedipine (Procardia®, Adalat®) DRUG INFO

Short-acting calcium channel blocker **(CCB)**. Decreases systemic vascular resistance. Increases cardiac index, CBF (by 10-20%), GFR, and Na excretion. Response some-what variable. Onset: 1-15 mins. Duration: 3-5 hrs.

SIDE EFFECTS: flushing H/A, palpitation, edema; reflex tachycardia, caution with beta blocker as negative inotropy may be additive. May cause severe hypotension in volume depleted patients (thus use with caution with mannitol or furosemide). May increase serum phenytoin (Dilantin®) levels. Use of short-acting CCBs may be associated with cardiac risk, thus long-acting agents should be used unless specific benefit outweighs the risk.

Rx 10-20 mg PO, faster onset with sublingual or buccal administration (puncture capsule), or if chewed (patient expels capsule after chewing). Note: the beneficial effects of the drug results from swallowing the capsule contents, the medication is not absorbed through the mucosa. If no response after 20-30 min, give additional 10 mg.

labetalol (Normodyne®, Trandate®) DRUG INFO

See page 20. Chronic administration may have higher incidence of orthostatic hypotension, fever, sexual dysfunction, and hepatic toxicity than other beta blockers.

metoprolol (Lopressor®) DRUG INFO

Beta blocker that is relatively cardioselective at doses < 200 mg. ***Rx*** 50-200 mg in 1 or 2 doses.

enalapril (Vasotec®) **DRUG INFO**

Angiotensin converting enzyme **(ACE)** inhibitor. Do not use during pregnancy. May be less effective in black patients. See *enalaprilat* above for IV use.

Rx initial dose 2.5-5 mg in one dose; maintenance 5-40 mg in 1 or 2 doses.

2.2.2. Hypotension (shock)

Classification:

1. hypovolemic: first sign usually tachycardia. > 20-40% of blood volume loss must occur before perfusion of vital organs is impaired. Includes:
   A. hemorrhage (external or internal)
   B. bowel obstruction (with third spacing)
2. septic: most often due to gram negative sepsis
3. cardiogenic: includes MI, cardiomyopathy, dysrhythmias (including A-fib)
4. neurogenic: e.g. paralysis due to spinal cord injury. Blood pools in venous capacitance vessels
5. miscellaneous
   A. anaphylaxis
   B. insulin reaction

CARDIOVASCULAR AGENTS FOR SHOCK

Plasma expanders. Includes:

1. crystalloids: normal saline has less tendency to promote cerebral edema than others (see *IV fluids*, page 878 under control of elevated ICP)
2. colloids: e.g. hetastarch (Hespan®). ✖ CAUTION: repeated administration over a period of days may prolong PT/PTT and clotting times and may increase the risk of rebleeding in aneurysmal SAH[40] (*see page 1042*)

3. blood products: expensive. Risk of transmissible diseases or transfusion reaction

dopamine DRUG INFO

See *Table 2-11* for a summary of the effects of dopamine **(DA)** at various dosages. DA is primarily a vasoconstrictor ($ß_1$ effects usually overridden by α–activity). 25% of dopamine given is rapidly converted to norepinephrine **(NE)**. At doses > 10 mcg/kg/min one is essentially giving NE. May cause significant hyperglycemia at high doses.

Rx Start with 2-5 mcg/kg/min and titrate.

Table 2-11 Dopamine dosage

Dose (mcg/kg/min)	Effect	Result
0.5-2.0 (sometimes up to 5)	dopaminergic	renal, mesenteric, coronary, & cerebral vasodilatation, (+) inotrope
2-10	$ß_1$	positive inotrope
> 10	α, ß & dopaminergic	releases nor-epi (vasoconstrictor)

dobutamine (Dobutrex®) DRUG INFO

Vasodilates by $ß_1$ (primary) and by increased CO from (+) inotropy ($ß_2$); result: little or no fall in BP, less tachycardia than DA. No alpha release nor vasoconstriction. May be used synergistically with nitroprusside. Tachyphylaxis after ≈ 72 hrs. Pulse increases > 10% may exacerbate myocardial ischemia, more common at doses > 20 mcg/kg/min. Optimal use requires hemodynamic monitoring. Possible platelet function inhibition.

Rx usual range 2.5-10 mcg/kg/min; rarely doses up to 40 used (to prepare: put 50 mg in 250 ml D5W to yield 200 mcg/ml).

amrinone (Inocor®) DRUG INFO

Nonadrenergic cardiotonic. Phosphodiesterase inhibitor, effects similar to

dobutamine (including exacerbation of myocardial ischemia). 2% incidence of thrombocytopenia.

Rx 0.75 mg/kg initially over 2-3 min, then drip 5-10 mcg/kg/min.

phenylephrine (Neo-Synephrine®) DRUG INFO

Pure alpha sympathomimetic. Useful in hypotension associated with tachycardia (atrial tachyarrhythmias). Elevates BP by increasing SVR via vasoconstriction, causes reflex increase in parasympathetic tone (with resultant slowing of pulse). Lack of ß action means non-inotropic, no cardiac acceleration, and no relaxation of bronchial smooth muscle. Cardiac output and renal blood flow may decrease. Avoid in spinal cord injuries (*see page 935*).

Rx pressor range: 100-180 mcg/min; maintenance: 40-60 mcg/min. To prepare: put 40 mg (4 amps) in 500 ml D5W to yield 80 mcg/ml; a rate of 8 ml/hr = 10 mcg/min.

norepinephrine DRUG INFO

Primarily vasoconstrictor (? counterproductive in cerebral vasospasm, ? decreases CBF). ß-agonist at low doses. Increases pulmonary vascular resistance.

epinephrine (adrenalin globally) DRUG INFO

Rx 0.5-1.0 mg of 1:10,000 solution IVP; may repeat q 5 minutes (may bolus per ET tube). Drip: start at 1.0 mcg/min, titrate up to 8 mcg/min (to prepare: put 1 mg in 100 ml NS or D5W).

isoproterenol (Isuprel®) DRUG INFO

Positive chronotropic and inotropic, → increased cardiac O_2 consumption, arrhythmias, vasodilatation (by $ß_1$ action) skeletal muscle > cerebral vessels.

levophed **DRUG INFO**

Direct ß stimulation (positive inotropic and chronotropic).

Rx start drip at 8-12 mcg/min; maintenance 2-4 mcg/min (0.5-1.0 ml/min) (to prepare: put 2 mg in 500 ml NS or D5W to yield 4 mcg/cc).

2.3. Sedatives & paralytics

Richmond agitation-sedation scale (RASS)

A validated scale[41, 42] that uses positive numbers for agitation and negative numbers for sedation as shown in *Table 2-12*. Useful for quantitating the desired level of sedation when titrating sedatives for agitated patients.

Procedure for performing RASS assessment:

1. on observation, patient is alert, restless or agitated: score 0 to +4
2. if patient is not alert, state patient's name and verbally instruct to open eyes and look at speaker: score –1 to –3
3. if no response to verbal stimulus, physically stimulate by shaking shoulder and/or sternal rub: score –4 or –5

Table 2-12 Richmond agitation-sedation scale

	Score	Term	Description	
AGITATION	+4	combative	overly combative, violent, immediate danger to staff	
AGITATION	+3	very agitated	pulls or removes tubes or catheters; aggressive	
AGITATION	+2	agitated	frequent non-purposeful movements, fights ventilator	
AGITATION	+1	restless	anxious, but movements not aggressive vigorous	
	0	alert & calm		
SEDATION	–1	drowsy	not fully alert, but has sustained awakening (eye-opening/contact) to *voice* (≥ 10 seconds)	verbal stimulation
SEDATION	–2	light sedation	briefly awakens with eye contact to *voice* (< 10 seconds)	verbal stimulation
SEDATION	–3	moderate sedation	movement or eye opening to *voice* (no eye contact)	verbal stimulation
SEDATION	–4	deep sedation	no response to voice, but movement or eye-opening to *physical* stimulation	physical stimulation
SEDATION	–5	unarousable	no response to *voice* or *physical* stimulation	physical stimulation

2.3.1. Conscious sedation

Use of these agents requires ability to provide immediate emergency ventilatory support (including intubation). Agents include:

- midazolam (Versed®): *see page 51*
- pentobarbital (Nembutal®): a barbiturate. ***Rx*** for 70 kg adult: 100 mg slow IVP

methohexital (Brevital®) DRUG INFO

More potent and shorter acting than thiopental (useful e.g. for percutaneous rhizotomy where patient needs to be sedated and awakened repeatedly). Lasts 5-7 min. Similar cautions with the added problem that methohexital may induce seizures. May no longer be available in the U.S.

Rx Adult: 1 gm% solution (add 50 ml diluent to 500 mg to yield 10 mg/ml), 2 ml test dose, then 5-12 ml IVP at rate of 1 ml/5 secs, then 2 to 4 ml q 4-7 min PRN.

haloperidol (Haldol®) DRUG INFO

SIDE EFFECTS: rare neuroleptic malignant syndrome. ✖ Contraindicated in Parkinson's disease. Anticholinergic effects may exacerbate urinary retention.

Rx For "rapid sequence tranquilization" (to sedate acutely agitated patient): 5-10 mg haloperidol IM q 15 minutes until patient controlled.

2.3.2. Sedation

Generally requires intubation and mechanical ventilatory support in the ICU. Doses are generally lower than those used by anesthesiologists for general anesthesia.

thiopental (Pentothal®) DRUG INFO

A short acting barbiturate. 1st dose causes unconsciousness in 20-30 secs (circulation time), depth increases up to 40 secs, duration = 5 mins (terminated by redistribution), consciousness returns over 20-30 mins.

SIDE EFFECTS: dose related respiratory depression, irritation if extravasated, intraarterial injection → necrosis, agitation if injected slowly, an antianalgesic, myocardial depressant, hypotension in hypovolemic patients.

Rx Adult: initial concentration should not exceed 2.5%, give 50 mg test dose moderately rapid IVP, then if tolerated give 100-200 mg IVP over 20-30 secs (500 mg may be required in large patient).

★ remifentanil (Ultiva®) DRUG INFO

Ultrashort acting micro-opioid receptor agonist. Potency similar to fentanyl. Rapidly crosses BBB. Onset: < 1 min. Offset: 3-10 mins. Lowers ICP. Metabolism: non-hepatic hydrolysis by nonspecific blood and tissue esterases, ∴ no accumulation. Synergy with thiopental, propofol, isoflurane, midazolam requires reducing doses of these agents by up to 75%. **SIDE EFFECTS:** bradycardia, hypotension (these side effects may be blunted by pretreatment with anticholinergics), N/V, muscle rigidity, pruritus (especially facial) dose dependent respiratory depression at doses > 0.05 mcg/kg/min.

Rx Adult: avoid bolus doses. Start with drip of 0.05 mcg/kg/min. Titrate in

0.025 mcg/kg/min increments to a maximum of 0.1-0.2 mcg/kg/min. Add a sedative if adequate sedation not achieved at maximum dose. Wean infusion in 25% decrements over 10 minutes after extubation. **SUPPLIED**: vials of 1, 2 or 5 mg powder to be reconstituted to 1 mg/ml solution.

fentanyl (Sublimaze®) DRUG INFO

Narcotic, potency ≈ 100 **x** morphine. High lipid solubility → rapid onset. Offset (small doses): 20-30 mins. Unlike morphine and meperidine, does not cause histamine release. Lowers ICP. **SIDE EFFECTS:** dose dependent respiratory depression, large doses given rapidly may cause chest wall rigidity. Repeated dosing may cause accumulation. Diminished sensitivity to CO_2 stimulation, may persist longer than the depression of respiratory rate (up to 4 hours).

Rx Adult: 25-100 mcg (0.5-2 ml) IVP, repeat PRN. **SUPPLIED**: 50 mcg/ml; requires refrigeration.

⭑ propofol (Diprivan®) DRUG INFO

A sedative hypnotic. Also useful in high doses during aneurysm surgery as a neuroprotectant (*see page 1064*). Protection seems to be less than with barbiturates. Offset time increases after ≈ 12 hours of use.

Rx for sedation: start at 5-10 mcg/kg/min. Increase by 5-10 mcg/kg/min q 5-10 minutes PRN desired sedation (up to a max of 50 mcg/kg/min).

SIDE EFFECTS: include **Propofol Infusion Syndrome**: hyperkalemia, hepatomegaly, lipemia, metabolic acidosis, myocardial failure, rhabdomyolysis, renal failure and sometimes death[43]. First identified in children, but may occur at any age. NB: metabolic acidosis of unknown etiology in a patient on propofol is propofol infusion syndrome until proven otherwise. Use with caution at doses > 50 mcg/kg/min or at any dose for > 48 hrs. Also note that the lipid carrier provides 1.1 kCal/ml and hypertriglyceridemia may occur.

SUPPLIED: 500 mg suspended in a 50 ml bottle of fat emulsion. The bottle and tubing must be changed every 12 hours since it contains no bacteriostatic agent.

★ Precedex® (dexmedetomidine) **DRUG INFO**

An alpha-2 adrenoceptor agonist. Acts in locus ceruleus and dorsal root ganglia. Has both sedative and analgesic properties and dramatically reduce the risk of respiratory depression and the amount of narcotic analgesics required. Reduces shivering.

Rx: usual loading dose is 1 mcg/kg IV over 10 minutes (loading dose not needed if patient already sedated with other agents), followed by continuous IV infusion of 0.2-1.0 mcg/kg/hr titrated to desired effect, not to exceed 24 hours (for short sedation or use as a "transition" drug). **SIDE EFFECTS:** clinically significant bradycardia and sinus arrest have occurred in young, healthy volunteers with increased vagal tone (anticholinergics such as atropine 0.2 mg IV or glycopyrrolate 0.2 mg IV may help). Use with caution in patients with advanced heart block, baseline bradycardia, using other drugs that lower heart-rate, and hypovolemia. **SUPPLIED**: 2 ml vials of 100 mcg/ml to be diluted in 48 ml NS for a final concentration of 4 mcg/ml for IV use.

2.3.3. Paralytics (neuromuscular blocking agents)

CAUTION: requires ventilation (intubation or Ambu-bag/mask). Reminder: paralyzed patients may still be conscious and therefore able to feel pain, the simultaneous use of sedation is thus required for conscious patients.

Early routine use in head-injured patients lowers ICP (e.g. from suctioning[44]) and mortality, but does not improve overall outcome[45].

Neuromuscular blocking agents **(NMBAs)** are classified clinically by time to onset and duration of paralysis as shown in *Table 3-13*. Additional information for some agents follows the table along with some considerations for neurosurgical patients.

Table 3-13 Onset and duration of muscle relaxants

Clinical class	Agent	Trade name (®)	Onset (min)	Duration (min)	Spontaneous recovery (min)	Comment
Ultra-short	succinylcholine	Anectine	1	5-10	20	shortest onset and duration; plasma cholinesterase dependent; many side effects
Short	rocuronium	Zemuron	1-1.5	20-35	40-60	close to succinylcholine in onset in large doses; some vagolytic action in children
Intermediate	atracurium	Tracrium	3-5	20-35	40-60	no renal or hepatic metabolism; histamine release in larger doses
	vecuronium	Norcuron	3-5	20-35	40-60	minimal cardiovascular side effects (bradycardia reported); no histamine release
	cisatracurium	Nimbex	1.5-2	40-60	60-80	no histamine release at recommended doses
Long	d-tubocurarine		4-6	45-60	60-180	histamine release; ↑ ICP; ganglion block
	metocurine	Metubine	4-6	45-60	60-180	fewer side effects than d-tubocurarine*
	pancuronium	Pavulon	4-6	45-60	60-180	cardiovascular side effects; vagolytic
	doxacurium	Nuromax	4-6	45-60	60-180	minimal cardiovascular side effects*

* not commonly used in ICU due to lack of clinical experience

ULTRA-SHORT ACTING PARALYTICS

succinylcholine (Anectine®) **DRUG INFO**

The only depolarizing ganglionic blocker (the rest are competitive blockers). Rapidly inactivated by plasma pseudocholinesterases. A single dose produces fasciculations then paralysis. Onset: 1 min. Duration of action: 5-10 min.

Indications

Due to significant side effects (*see below*), use is now limited primarily to the following indications. Adults: generally recommended only for emergency intubations where the airway is not controlled. In children: only when intubation is needed with a full stomach, or if laryngospasm occurs during attempted intubation using other agents.

Side effects

✖ CAUTIONS: usually increases serum K^+ by 0.5 mEq/L (on rare occasion causes severe hyperkalemia ($[K^+]$ up to 12 mEq/L) in patients with neuronal or muscular pathology, causing cardiac complications which cannot be blocked),

therefore contraindicated in acute phase of injury following major burns, multiple trauma or extensive denervation of skeletal muscle or upper motor neuron injury. Do not use for routine intubations in adolescents and children (may cause cardiac arrest even in apparently healthy youngsters, many of whom have undiagnosed myopathies). Linked to malignant hyperthermia (*see page 5*).

May cause dysrhythmias, especially sinus bradycardia (treat with atropine). May get autonomic stimulation from ACh-like action → HTN, and brady- or tachycardia (especially in peds with repeated doses). The fasciculations may increase ICP, intragastric pressure, and intraocular pressure (contraindicated in penetrating eye injury, especially to anterior chamber; OK in glaucoma).

Precurarization with a "priming dose" of a nondepolarizing blocker (usually ≈ 10% of the intubating dose, e.g. pancuronium 0.5-1 mg IV 3-5 minutes prior to succinylcho-line) in patients with elevated ICP or increased intraocular pressure (to ameliorate further pressure increases during fasciculation phase) and in patients who have eaten recently (controversial[46]). Phase II block (similar to nondepolarizing blocker) may develop with excessive doses or in patients with abnormal pseudocholinesterase.

Dosing

***Rx* Adult**: 0.6-1.1 mg/kg (2-3 ml/70 kg) IVP (err on high side to allow time for procedure & to avoid multi-dosing complications), may repeat this dose **x** 1.

***Rx* Peds** (CAUTION: Not recommended for routine use, *see above*) Children: 1.1 mg/kg. Infants (< 1 mos): 2 mg/kg.

SUPPLIED: 20 mg/ml concentration.

SHORT ACTING PARALYTICS

rocuronium (Zemuron®) DRUG INFO

In large doses, has speed of onset that approaches succinylcholine. However, in these doses, paralysis usually lasts ≈ 1-2 hrs. Expensive.

***Rx* Adult**: initial dose 0.6-1 mg/kg. May be used as infusion of 10-12 mcg/kg/min.

INTERMEDIATE ACTING PARALYTICS

⋆ vecuronium (Norcuron®) DRUG INFO

Nondepolarizing (competitive) NMBA. Adequate paralysis for intubation within 2.5-3 minutes of administration. About one third more potent than pancuronium, shorter duration of action (lasts ≈ 30 minutes after initial dose). Unlike pancuronium, very little vagal (i.e. cardiovascular) effects. No CNS active metabolites. Does not affect ICP or CPP. Hepatically metabolized. Due to active metabolites, paralysis has been reported to take 6 hrs to 7 days to recede following discontinuation of the drug after ≥ 2 days use in patients with renal failure[47]. Must be mixed to use.

Dosing

Supplied: 10 mg freeze-dried cakes requiring reconstitution. Use within 24 hrs.

Rx Adult and children > 10 years age: 0.1 mg/kg (for most adults use 8-10 mg as initial dose). May repeat q 1 hr PRN. Infusion: 1-2 mcg/kg/min.

Rx Pediatric: children (1-10 yrs) require slightly higher dose and more frequent dosing than adult. Infants (7 weeks - 1 yr): slightly more sensitive on a mg/kg basis than adults, takes ≈ 1.5 **x** longer to recover. Use in neonates and continuous infusion in children is insufficiently studied.

⋆ cisatracurium (Nimbex®) DRUG INFO

Nondepolarizing (competitive) blocker. This isomer of atracurium does not release histamine unlike its parent compound (*see below*). Provides about 1 hour of paralysis. Also undergoes Hofmann degradation, with laudanosine as one of its metabolites.

Rx Adult and children > 12 years age: 0.15 or 0.2 mg/kg as part of propofol/nitrous oxide/oxygen induction-intubation technique produces muscle paralysis adequate for intubation within 2 or 1.5 minutes, respectively. Infusion: 1-3 mcg/kg/min.

Rx Pediatric: children (2-12 yrs): 0.1 mg/kg given over 5-10 seconds during inhalational or opioid anesthesia.

atracurium (Tracrium®) DRUG INFO

Nondepolarizing (competitive) blocker. After IV bolus: onset 2-2.5 mins, peak 3-5 mins, duration 15-20 mins (initial dose may last up to 30 minutes). Undergoes nonenzymatic Hofmann degradation and ester hydrolysis at normal physiologic pH and temperature, inactivating the drug in ≈ 30 minutes. Therefore useful in patients with liver or renal failure. Reversible with neostigmine (*see below*). Causes histamine release which can produce hypotension (consider cisatracurium instead, *see above*). A metabolite, laudanosine, is neuroexcitatory, and accumulation could theoretically cause seizures (no documented cases)[46].

Dosing

SUPPLIED: 5 & 10 ml ampules of 10 mg/ml concentration.

Rx Adult & children > 2 yrs age: 0.4-0.5 mg/kg IVP. Reduce subsequent doses to 0.02 mg/kg.

Rx Neonates (1 month - 2 yrs): 0.3-0.4 mg/kg.

LONG ACTING PARALYTICS

pancuronium (Pavulon®) DRUG INFO

The "prototype" nondepolarizing (competitive) paralytic. Peak: 3-5 mins, duration up to 60 mins. Reversible with anticholinesterases such as neostigmine (*see below*). Renal elimination.

SIDE EFFECTS: usefulness is limited because the drug is vagolytic and an indirect sympathomimetic which increases cardiac output, pulse rate and ICP. Consider vecuronium as an alternative (*see above*).

Dosing

Rx Adult & children: 0.04-0.10 mg/kg IVP (start with 3 mg). Reduce subsequent doses to 0.02 mg/kg.

Rx Neonates: especially sensitive, test dose 0.02 mg/kg.

REVERSAL OF COMPETITIVE MUSCLE BLOCKADE

It takes ≈ 20 minutes for full reversal of pancuronium (Pavulon®) (depending on the amount of time since the last dose). Reversal is usually not attempted until patient has at least 1 twitch to a train of 4 stimulus, otherwise

reversal may be incomplete if patient is profoundly blocked and blockade may reoccur as the reversal wears off

1. neostigmine (Prostigmin®): 2.5 mg (minimum) to 5 mg (maximum) IV (start low, no efficacy from > 5 mg and can produce severe weakness especially if the maximum dose is exceeded in the absence of neuromuscular blockade)

PLUS (to prevent bradycardia…), EITHER

• 0.5 mg atropine for each mg of neostigmine

OR

• 0.2 mg glycopyrrolate (Robinul®) for each mg of neostigmine

2.4. Neurogenic pulmonary edema

A rare condition associated with a variety of intracranial pathologies, including: subarachnoid hemorrhage, generalized seizures, and head injury.

Pathophysiology

Two possibly synergistic mechanisms. Sudden increased ICP or hypothalamic injury may produce a salvo of sympathetic discharge causing redistribution of blood to the pulmonary circulation, resulting in elevation of pulmonary capillary wedge pressures **(PCWP)** and increased permeability. Secondly, the associated surge of catecholamines directly disrupts the capillary endothelium which increases alveolar permeability.

Treatment

Supportive, using measures such as positive pressure ventilation with low levels of PEEP (*see page 880*) and treatment to normalize ICP. A PA-catheter is usually helpful.

There may be some efficacy in using a dobutamine infusion[48] supplemented with furosemide as needed. The theoretical advantage of dobutamine over previously attempted alpha- and beta-blockers is that dobutamine does not reduce cerebral perfusion. Nitroprusside may help dilate the pulmonary vasculature.

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NOTES

3. General care

3.1. Endocrinology

3.1.1. Steroids

3.1.1.1. Replacement therapy

Under normal, basal conditions, the adrenal cortex secretes 15-25 mg/day of **cortisol** (hydrocortisone is the name for the identical pharmaceutical compound for administration), and 1.5-4 mg/day of **corticosterone**. Cortisol has a half-life of ≈ 90 minutes.

In primary adrenocortical insufficiency (Addison's disease), both glucocorticoids and mineralocorticoids must be replaced. In secondary adrenal insufficiency caused by deficient corticotropin **(ACTH)** release by the pituitary, mineralocorticoid secretion is usually normal and only glucocorticoids need to be replaced.

Table 3-1 shows equivalent daily corticosteroid doses for replacement therapy.

Table 3-1 Equivalent corticosteroid doses*

Steroid: generic (proprietary)	Equiv dose (mg)	Route	Dosing	Mineralo-corticoid potency	Oral dosing forms
cortisone (Cortone®)	25	PO, IM	2/3 in AM, 1/3 in PM	2+	tabs: 5, 10 & 25 mg
hydrocortisone AKA cortisol (Cortef®)	20	PO	2/3 in AM, 1/3 in PM	2+	tabs: 5, 10 & 20 mg
(Solu-Cortef®)		IV, IM†			
prednisone (Deltasone®)	5	PO only	divided BID-TID	1+	tabs: 1, 2.5, 5, 10, 20, 50 mg‡
methylprednisolone (Solumedrol®)	4	PO, IV, IM		0	tabs§: 2, 4, 8, 16, 24, 32 mg
dexamethasone (Decadron®)	0.75	PO, IV	divided BID-QID	0	scored tabs: 0.25, 0.5, 0.75, 1.5, 4, 6 mg

* doses given are daily doses. Steroids listed are used primarily as glucocorticoids: equivalent glucocorticoid PO or IV dose is given; IM may differ

† IM route recommended only for emergencies where IV access cannot be rapidly obtained

‡ Sterapred Uni-Pak® contains 21 tabs of 5 mgs prednisone and tapers dosage from 30 to 5 mgs over 6 days; "DS" contains 10 mg tabs and tapers from 60 mg to 10 mg over 6 days; "DS 12-Day" contains 48 10 mg tabs and tapers from 60 mg to 20 mg over 12 days

§ Medrol Dosepak® contains 21 tabs of 4 mgs methylprednisolone and tapers dosage from 24 mg/d to 4 mg/d over 6 days

Physiologic replacement (in the absence of stress) can be accomplished with either:

1. hydrocortisone: 20 mg PO q AM and 10 mg PO q PM
2. or prednisone: 5 mg PO q AM and 2.5 mg PO q PM

Cortisol and cortisone are useful for chronic primary adrenocortical insufficiency or for Addisonian crisis. Because of mineralocorticoid activity, use for chronic therapy of other conditions (e.g. hypopituitarism) may result in salt and fluid retention, hypertension and hypokalemia.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS SUPPRESSION

Chronic steroid administration suppresses the hypothalamic-pituitary-adrenal **(HPA)** axis, and eventually causes adrenal atrophy. If steroids are abruptly stopped or if acute illness develops, symptoms of adrenocortical insufficiency **(AI)** may ensue (*see Table 3-2*), which if severe may progress to Addisonian crisis (*see page 34*). Recovery of adrenal cortex lags behind the pituitary, so basal ACTH levels increase before cortisol levels.

HPA suppression depends on the specific glucocorticoid used, the route,

frequency, time, and duration of treatment. Suppression is unlikely with < 40 mg prednisone (or equivalent) given in the morning for less than ≈ 7 days, or with every-other-day therapy of < 40 mg for ≈ 5 weeks[1]. Some adrenal atrophy may occur after 3-4 days of high dose steroids, and some axis suppression will almost certainly occur after 2 weeks of 40-60 mg hydrocortisone (or equivalent) daily. After a month or more of steroids, the HPA axis may be depressed for as long as one year.

Measuring morning plasma hydrocortisone can evaluate the degree of recovery of basal adrenocortical function, but does not assess adequacy stress response.

Table 3-2 Symptoms of adrenal insufficiency (AI)

• fatigue • weakness • arthralgia • anorexia • nausea • hypotension	• orthostatic dizziness • hypoglycemia • dyspnea • Addisonian crisis (if severe; with risk of death, *see page 34*)

STEROID WITHDRAWAL[1]

In addition to the above dangers of hypocortisolism in the presence of HPA suppression, too rapid a taper may cause a flare-up of the underlying condition for which steroids were prescribed.

When the risk of HPA suppression is low (as is the case with short courses of steroids for less than ≈ 5-7 days[2] generally prescribed for most neurosurgical indications) abrupt discontinuation usually carries a low risk of AI. For up to≈ 2 weeks of use, steroids are usually safely withdrawn by tapering over 1-2 weeks. For longer treatment, or when withdrawal problems develop, use the following conservative taper:

1. make small decrements (equivalent to 2.5-5 mg prednisone) every 3-7 d. Patient may experience mild withdrawal symptoms of[3]:
   A. fatigue
   B. anorexia
   C. nausea
   D. orthostatic dizziness
2. “backtrack” (i.e. increase the dose and resume a more gradual taper) if any of the following occur:
   A. exacerbation of the underlying condition for which steroids were used
   B. evidence of steroid withdrawal symptoms (*see Table 3-2*)

C. intercurrent infection or need for surgery (see *Stress doses* below)

3. once "physiologic" doses of glucocorticoid have been reached (about 20 mg hydrocortisone/day or equivalent (*see Table 3-1*)):
   A. the patient is switched to 20 mg hydrocortisone PO q AM (do not use long acting preparations)
   B. after ≈ 2-4 weeks, a morning cortisol level is checked (prior to the AM hydrocortisone dose), and the hydrocortisone is tapered by 2.5 mg weekly until 10 mg/d is reached (lower limits of physiologic)
   C. then, every 2-4 weeks, the AM cortisol level is drawn (prior to AM dose) until the 8 AM cortisol is > 10 mcg/100 ml, indicating return of baseline adrenal function
   D. when this return of baseline adrenal function occurs:
      1. daily steroids are stopped, but stress doses must still be given when needed (*see below)*
      2. monthly cosyntropin stimulation tests (*see page 647*) are performed until normal. The need for stress doses of steroids ceases when a positive test is obtained. The risk for adrenal insufficiency persists ≈ <u>2 years</u> after cessation of chronic steroids (especially the first year)

STRESS DOSES

During physiologic "stress" the normal adrenal gland produces ≈ 250-300 mg hydrocortisone/day. With chronic glucocorticoid therapy (either at present, or within last 1-2 yrs), suppression of the normal "stress-response" necessitates supplemental doses.

In patients with a suppressed HPA axis:

- for mild illness (e.g. UTI, common cold), single dental extraction: double the daily dose (if off steroids, give 40 mg hydrocortisone BID)
- for moderate stress (e.g. flu), minor surgery under local anesthesia (endoscopy, multiple dental extractions…): give 50 mg hydrocortisone BID
- for major illness (pneumonia, systemic infections, high fever), severe trauma, or emergency surgery under general anesthesia: give 100 mg hydrocortisone IV q 6-8 hrs for 3-4 days until the stress is resolved
- for elective surgery, *see Table 3-3* for guidelines

Table 3-3 Steroid stress doses for elective surgery

On day of surgery, 50 mg cortisone acetate IM, followed by 200 mg hydrocortisone IV infused over 24 hrs

Post-op day	Hydrocortisone (mg)		
	8 AM	4 PM	10 PM
1	50	50	50
2	50	25	25
3	40	20	20
4	30	20	10
5	25	20	5
6	25	15	–
7	20	10	–

POSSIBLE DELETERIOUS SIDE EFFECTS OF STEROIDS

Although these side effects are more common with prolonged administration[4], some can occur even with short treatment courses. Some evidence suggests that low-dose glucocorticoids (≤ 10 mg/d of prednisolone or prednisone equivalent) for rheumatoid arthritis does not increase osteoporotic fractures, blood pressure, cardiovascular disease, or peptic ulcers[5], but weight gain and skin changes are common. Possible side effects include[3, 6]:

- cardiovascular and renal
  - hypertension
  - sodium and water retention
  - hypokalemic alkalosis
- CNS
  - progressive multifocal leukoencephalopathy **(PML)** (*see page 364*)
  - mental agitation or "steroid psychosis"
  - spinal cord compression from spinal epidural lipomatosis: rare (*see page 1186*)
  - pseudotumor cerebri (see *Idiopathic intracranial hypertension (IIH)*, page 713)
- endocrine
  - caution: because of growth suppressant effect in children, daily glucocorticoid dosing over prolonged periods should be reserved for the most urgent indications
  - secondary amenorrhea
  - suppression of hypothalamic-pituitary-adrenal axis: reduces endogenous steroid production → risk of adrenal insufficiency with steroid withdrawal

(*see above*)
- ♦ Cushingoid features with prolonged usage (iatrogenic Cushing's syndrome): obesity, hypertension, hirsutism…

• GI: risk increased only with steroid therapy > 3 weeks duration and regimens of prednisone > 400-1000 mg/d or dexamethasone > 40 mg/d[7]
- ♦ gastritis and steroid ulcers: incidence lowered with the use of antacids and/or H_2 antagonists (e.g. cimetidine, ranitidine…)
- ♦ pancreatitis
- ♦ intestinal or sigmoid diverticular perforation[8]: incidence ≈ 0.7%. Since steroids may mask signs of peritonitis, this should be considered in patients on steroids with abdominal discomfort, especially in the elderly and those with a history of diverticular disease. Abdominal x-ray usually shows free intraperitoneal air

• inhibition of fibroblasts
- ♦ impaired wound healing or wound breakdown
- ♦ subcutaneous tissue atrophy

• metabolic
- ♦ glucose intolerance (diabetes) and disturbance of nitrogen metabolism
- ♦ hyperosmolar nonketotic coma
- ♦ hyperlipidemia
- ♦ tend to increase BUN as a result of protein catabolism

• ophthalmologic
- ♦ posterior subcapsular cataracts
- ♦ glaucoma

• musculoskeletal
- ♦ avascular necrosis **(AVN)** of the hip or other bones: usually with prolonged administration → cushingoid habitus and increased marrow fat within the bone[9]
- ♦ osteoporosis: may predispose to vertebral compression fractures which occur in 30-50% of patients on prolonged glucocorticoids (*see page 992*). Steroid induced bone loss may be reversed with cyclical administration of etidronate[10] in 4 cycles of 400 mg/d **x** 14 days followed by 76 days of oral calcium supplements of 500 mg/d (not proven to reduced rate of VB fractures, *see page 992*)
- ♦ muscle weakness (steroid myopathy): often worse in proximal muscles

• infectious
- ♦ immunosuppression: with possible superinfection, especially fungal, parasitic

  - possible reactivation of TB, chickenpox
- hematologic
  - hypercoagulopathy from inhibition of tissue plasminogen activator
  - steroids cause demargination of white blood cells, which may artifactually elevate the WBC count even in the absence of infection
- miscellaneous
  - hiccups: may respond to chlorpromazine (Thorazine®) 25-50 mg PO TID-QID **x** 2-3 days (if symptoms persist, give 25-50 mg IM)
  - steroids readily cross the placenta, and fetal adrenal hypoplasia may occur with the administration of large doses during pregnancy

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3.1.1.2. Hypocortisolism

8 A.M. serum cortisol is the best way to test for hypocortisolism.

ADDISONIAN CRISIS

An adrenal insufficiency emergency.

Symptoms: mental status changes (confusion, lethargy, or agitation), muscle weakness.

Signs: postural hypotension or shock, hyperthermia (as high as 105° F, 45.6 C)

Labs: hyponatremia, hyperkalemia, hypoglycemia.

TREATMENT OF ADDISONIAN CRISIS

If possible, draw serum for cortisol determination (do <u>not</u> wait for these results to institute therapy). Give fluids sufficient for dehydration and shock.

For “glucocorticoid emergency”

- hydrocortisone sodium succinate (Solu-Cortef®): 100 mg IV STAT and then 50 mg IV q 6 hrs

AND

- cortisone acetate 75-100 mg IM STAT, and then 50-75 mg IM q 6 hrs

For “mineralocorticoid emergency”

Usually not necessary in secondary adrenal insufficiency (e.g. panhypopituitarism)

• desoxycorticosterone acetate (Doca®): 5 mg IM BID
OR
• fludrocortisone (Florinef®): 0.05- 0.2 mg PO q d

NOT recommended for emergency treatment

✖ methylprednisolone

3.2. Hematology

3.2.1. Blood component therapy

PLATELETS

Normal platelet count **(PC)** is 150K-400K[A]. Thrombocytopenia is defined as PC < 150K. Bleeding (spontaneously or with invasive procedures) is rarely a problem with PC > 50K. Spontaneous hemorrhage is very likely with PC < 5K. Spontaneous intracranial hemorrhage is uncommon with PC > 30K, and is more common in adults than children. Based on patients with ITP, the risk of fatal hemorrhage in patients with PC < 30K is 0.0162-0.0389 cases per patient-year[11] (risk of death from infection is higher). Intracranial bleeding is usually subarachnoid or intraparenchymal, with petechial hemorrhages common.

A. abbreviation used here: 150K = 150,000/mm^3 = 150 **x** 109/l

Platelet therapy

1 unit of platelets contains 5.5 **x** 1010 (minimum) to 10 **x** 1010 platelets. The volume of 6 units is 250-300 ml. Platelets may be stored up to 5 days.

Recommended transfusion criteria[12]:

1. thrombocytopenia due to ↓ production (with or without increased destruction) (the most common causes are aplastic anemia and leukemia)
   A. PC < 10K even if no bleeding (prophylactic transfusion to prevent bleeding)

B. PC < 20K and bleeding

C. PC < 30K and patient at risk for bleeding: complaints of H/A, presence of confluent (c.f. scattered) petechiae, continuous bleeding from a wound, increasing retinal hemorrhage

D. PC < 50K *AND*

1. major surgery planned within 12 hours
2. PC rapidly falling
3. patient < 48 hours post-op
4. patient requires lumbar puncture
5. acute blood loss of > 1 blood volume in < 24 hours

2. platelet transfusions have limited usefulness when thrombocytopenia is due to platelet destruction (e.g. by antibodies as in ITTP) or consumption (if production is adequate or increased, platelet transfusion usually will not be useful)
3. documented platelet dysfunction in a patient scheduled for surgery or in a patient with advanced hepatic and/or renal insufficiency (consider pharmacologic enhancement of platelet function, e.g. desmopressin[13])

Other indications for platelet transfusion:

1. patients who have been on Plavix® or aspirin who need urgent surgery that cannot be postponed for ≈ 5 days to allow new platelets to be synthesized

Dosage

Approximately 25% of platelets are lost just with transfusion.

Peds: 1 U/m^2 raises PC by ≈ 10K, usually give 4 U/m^2.

Adult: 1 U raises platelet count by ≈ 5-10K. Typical dose for thrombocytopenic bleeding adult: 6-10 U (usual order: “8-pack”). Alternatively, 1 U of pheresed platelets may be given (obtained from a single donor by apheresis, equivalent to 8-10 U of pooled donor platelets).

Check PC 1-2 hrs after transfusion. The increase in PC will be less in DIC, sepsis, splenomegaly, with platelet antibodies, or if the patient is on chemotherapy. In the absence of increased consumption, platelets will be needed q 3-5 days.

PLASMA PROTEINS

FFP (FRESH FROZEN PLASMA)

1 bag = 200-250 ml (usually referred to as a "unit", not to be confused with 1 unit of *factor activity* which is defined as 1 ml). FFP is plasma separated from RBCs and platelets, and contains all coagulation factors and natural inhibitors. FFP has an out-date period of 12 months. The risk of AIDS and hepatitis for each unit of FFP is equal to that of a whole unit of blood.

Recommended transfusion criteria (modified[12]):

1. history or clinical course suggestive of coagulopathy due to congenital or acquired coagulation factor deficiency with active bleeding or pre-op, with PT > 18 sec or APTT > 1.5 **x** upper limit of normal (usually > 55 sec), fibrinogen functioning normally and level > 1 g/l, and coagulation factor assay < 25% activity
2. proven coagulation factor deficiency with active bleeding or scheduled for surgery or other invasive procedure
   A. congenital deficiency of factor II, V, VII, X, XI or XII
   B. deficiency of factor VIII or IX if safe replacement factors unavailable
   C. von Willebrand's disease unresponsive to DDAVP
   D. multiple coagulation factor deficiency as in hepatic dysfunction, vitamin K depletion or DIC
3. reversal of warfarin (Coumadin®) effect (PT > 18 sec, or INR > 1.6) in patient actively bleeding or requiring emergency surgery or procedure with insufficient time for vitamin K to correct (which usually requires > 6-12 hrs) (*see page 40*)
4. deficiency of antithrombin III, heparin cofactor II, or protein C or S
5. massive blood transfusion: replacement of > 1 blood volume (≈ 5 L in 70 kg adult) within several hours with evidence of coagulation deficiency as in (1) and with continued bleeding
6. treatment of thrombotic thrombocytopenic purpura, hemolytic uremic syndrome
7. ✖ because of associated hazards and suitable alternatives, the use of FFP as a volume expander is relatively contraindicated

Dosage: Usual starting dose is 2 bags of FFP (400-600 ml). If PT is 18-22 secs or APTT is 55-70 secs, 1 bag may suffice. Doses as high as 10-15 ml/kg may be needed for some patients. Monitor PT/PTT (or specific factor assay) and clinical bleeding. Since factor VII has a shorter half-life (≈ 6 hrs) than the other factors, PT may become prolonged before APTT.

Remember: if patient is also receiving platelets, that for every 5-6 units of platelets the patient is also receiving coagulation factors equivalent to ≈ 1 bag of

FFP.

ALBUMIN AND PLASMA PROTEIN FRACTION (PPF, AKA PLASMANATE®)

Usually from outdated blood, treated to inactivate hepatitis B virus. Ratio of albumin:globulin percentage in "albumin" is 96%:4%, in PPF it is 83%:17%. Available in 5% (oncotically and osmotically equivalent to plasma) and 25% (contraindicated in dehydrated patients). 25% albumin may be diluted to 5% by mixing 1 volume of 25% albumin to 4 volumes of D5W or 0.9% NS (✖ caution: mixing with sterile water will result in a hypotonic solution that can cause hemolysis and possible renal failure).

Expensive for use simply as a volume expander (≈ $60-80 per unit). Indicated only when total protein < 5.2 gm% (otherwise, use crystalloid which is equally effective). Rapid infusion (> 10 cc/min) has been reported to cause hypotension (due to Naacetate and Hegeman factor fragments). Use in ARDS is controversial. In neurosurgical patients, may be considered as an adjunct for volume expansion (along with crystalloids) for hyperdynamic therapy (*see page 1052*) when the hematocrit is < 40% following SAH where there is concern about increasing the risk of rebleeding e.g. with the use of hetastarch (*see page 1042*).

CRYOPRECIPITATE

Recommended transfusion criteria:

1. hemophilia A
2. von Willebrand disease
3. documented fibrinogen/factor VIII deficiency
4. documented disseminated intravascular coagulation (DIC): along with other modes of therapy

3.2.2. Coagulation

3.2.2.1. Anticoagulation

ANTICOAGULANT CONSIDERATIONS IN NEUROSURGERY

Most of these issues have not been studied in a rigorous, prospective fashion. Yet, these questions frequently arise. The following is to be considered a framework of guidelines, and is not to be construed as a standard of care. Table

3-4 acts as an index to the topics discussed below. Grayed cells are for future determination.

Contraindications to heparin

Contraindications to heparin therapy are constantly being reevaluated. Massive PE producing hemodynamic compromise should be treated with anticoagulation in most cases despite intracranial risks. Contraindications to full anticoagulation with heparin include:

- recent severe head injury
- recent craniotomy: *see below*
- patients with coagulopathies
- hemorrhagic infarction
- bleeding ulcer or other inaccessible bleeding site
- uncontrollable hypertension
- severe hepatic or renal disease
- < 4-6 hours before an invasive procedure (*see below*)
- brain tumor: *see below*

Table 3-4 Anticoagulation issues in neurosurgery

Issue	Page
General neurosurgical contraindications to full anticoagulation with heparin	36
Starting/continuing anticoagulation in the presence of the following neurosurgical conditions	
• incidental aneurysm	37
• subarachnoid hemorrhage	37
• brain tumor	37
• following craniotomy	37
• ischemic stroke • after tAP • for prevention of	1017 1011
• intracerebral hemorrhage	1127
Managing patients who are already anticoagulated who need a neurosurgical procedure	
• warfarin (Coumadin®)	37
• heparin	38
• LMW-heparin	38
• antiplatelet drugs (aspirin, Plavix, NSAIDs)	38

Patients with unruptured (incidental) cerebral aneurysms

Anticoagulation may not increase the risk of hemorrhage (i.e. rupture), however, should rupture occur, anticoagulation would most likely increase volume of hemorrhage and thus increase morbidity and mortality.

The decision to start/continue anticoagulant depends on the indication for the drugs, the size of the aneurysm (a small aneurysm < 4 mm is not as worrisome). Patients needing Plavix® for drug-eluting cardiac stents should probably be left on their drugs.

Patients on anticoagulation/antiplatelet drugs who develop SAH

Coumadin and antiplatelet drugs are usually reversed.

In patients with brain tumor

Some authors are reluctant to administer full-dose heparin to a patient with a brain tumor[14], although a number of studies found no higher risk in these patients when treated with heparin or oral anticoagulation[15-17] (PT should be followed very closely, one study recommended maintaining PT ≈ 1.25 **x** control[17]).

Post-operatively following craniotomy

Requires individualization based on the reason for the craniotomy. Surgery for parenchymal lesions where the surgery disrupts small vessels (e.g. brain tumor) is probably higher risk for hemorrhage than e.g. aneurysm surgery (expert opinion). Options:

Full anticoagulation: most neurosurgeons would probably not *fully* anticoagulate patients < 3-5 days following craniotomy[18], and some recommend at least 2 weeks. How-ever, one study found no increased incidence of bleeding when anticoagulation was resumed 3 days post craniotomy[19].

Low-dose anticoagulation: either with mini-dose heparin (5000 U SQ 2 hrs prior to craniotomy and continuing q 12 hrs post-op **x** 7 d[A]) or enoxaparin

(Lovenox)[B] (30 mg SQ BID or as a single dose of 40 MG SQ q d).

A. RPDB study[20]: assessed safety (not efficacy), 55 patients undergoing craniotomy for tumor received mini-dose heparin as indicated had no increased bleeding tendency by any of the parameters measured

B. RPNB study[21]: incidence of post-op hemorrhage increased to 11% with enoxaparin

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MANAGEMENT OF ANTICOAGULANTS PRIOR TO NEUROSURGICAL PROCEDURES

Warfarin

Management guidelines: Patients on warfarin who must be anticoagulated as long as possible (e.g. mechanical heart valves) may stop warfarin at least **3 days** prior to the procedure, and begin self-administered LMW heparin injections (e.g. Lovenox, *see page 39*) which are discontinued as outlined below (see *Low-molecular weight heparins (LMWH)*).

Patients with less critical anticoagulation needs (e.g. chronic a-fib) can usually stop the warfarin at least 4-5 days before the procedure, and a PT/INR is then checked on admission to the hospital. Patients must be advised that during the time that they are not anticoagulated, they are at risk of possible complications from the condition for which they are receiving the agents (annual risk for mechanical valve: ≈ 6%; for a-fib: depends on several factors including age & history of prior stroke, an average for patients > 65 years age is ≈ 5-6% (for details, *see page 1022*)).

For non-emergent neurosurgical procedures: For procedures where post-op mass effect from bleeding would pose serious risk (which includes most neurosurgical operations), it is recommended that the **PT should be ≈ ≤ 13.5 sec** (i.e. ≤ upper limits of normal) or the **INR should be ≈ ≤ 1.4** (e.g. for reference, this INR is considered safe for performing a percutaneous needle liver biopsy). To reverse anticoagulants, *see page 40*.

For emergent neurosurgical procedures:, Give FFP (start with 2 units) and vitamin K (10-20 mg IV at ≤ 1 mg/min) as soon as possible (*see page 40* for reversal of anticoagulation). The timing of surgery is then based on the urgency of the situation and the nature of the procedure (e.g. the decision might be to evacuate a spinal epidural hematoma in an acutely paralyzed patient before anticoagulation is fully reversed).

Heparin

For emergencies: if it would be deleterious to wait 4-6 hours after discontinuing heparin and then repeating the PTT to verify that anticoagulation has been corrected, then heparin can be reversed with protamine (*see page 41*).

For non-emergencies:

IV heparin: stop the drip ≈ 4-6 hours prior to the planned procedure. Option: recheck PTT just prior to starting the procedure.

"Mini-dose" SQ heparin: not mandatory to stop for craniotomy[A], but if desired to discontinue, then give last dose ≥ 12 hours prior to surgery.

Low-molecular weight heparins (LMWH)

For emergencies: can be reversed with protamine (*see page 41*).

Non-emergencies: 24-48° after the last dose is usually safe for surgery. Longer time is needed in renal failure. A factor Xa level can be used to check anticoagulation status, but this usually must be sent out, making it unsuitable for acute management.

Antiplatelet drugs and neurosurgical procedures

Plavix® (clopidogrel) (*see page 1147*) and **aspirin** cause permanent inhibition of platelet function that persists ≈ 5 days after discontinuation of the drug and can increase the risk of bleeding. For elective cases, 5-7 days off these drugs is recommended (surveys of German neurosurgeons[22, 23]: an average of 7 days was used for low-dose ASA, with a few who do spine surgery even while the patient is on ASA).

Cardiac stents: dual antiplatelet therapy (e.g. ASA + Plavix®) are mandatory for 4 weeks (90 days is preferable[24]) after placement of a bare metal cardiac stent, and for at least 1 year with drug-eluting stents **(DES)**[25]. Even short gaps in drug therapy (e.g. to perform neurosurgical procedures) is associated with significant risk of acute stent occlusion (and therefore elective surgery during this time is discouraged[26]). DES are so effective in suppressing endothelialization that lifetime dual antiplatelet therapy may be required. Bridging DES patients with antithrombin, anticoagulants, or glycoprotein IIb/IIIa agents has not been proven effective[26].

Reversal of antiplatelet drugs: While heparin and warfarin can be reliably and measurably reversed, the situation is less clear with antiplatelet agents[27]. Agents

used preop to reverse these drugs include: Desmopressin (DDAVP®)[22, 23] (*see* *page 41*) and FFP[22].

Reversal of Plavix for emergency surgery: platelets may be given (*see* *page 35*), however, Plavix effects persists for up to a couple of days after the last dose, and can actually inhibit platelets given *after* the drug is discontinued (the half-life of aspirin is lower and should not be an issue after 1 day). In cases with continued oozing in the first day or so after discontinuing Plavix, the following regimen is an option:

1. recombinant activated coagulation factor VII **(rFVIIa)**: even though the defect is in the platelets, rFVIIa works, via a mechanism not mediated by protein clotting factors. Very expensive (≈ $10,000 per dose), but this must be balanced against the cost of repeat craniotomy, increased ICU stay and additional morbidity
   - A. initial dose[28]: 90-120 mcg/kg
   - B. same dose 2 hrs later
   - C. 3rd dose 6 hrs after initial dose
2. platelets every 8 hours for 24 hours, <u>either</u>
   - A. 6 U of regular platelets
   - B. if patient is on fluid or volume restriction: 1 unit of pheresed platelets

Anticoagulants

For platelet function inhibitors, *see* *page 1146*.

warfarin (Coumadin®) **DRUG INFO**

An oral vitamin K antagonist. To anticoagulate average weight patient, give 10 mg PO q d **x** 2-4 days, then ≈ 5 mg q d. Follow coagulation studies, titrate to PT = 1.2-1.5 **x** control (or INR ≈ 2-3) for most conditions (e.g. DVT, single TIA). Higher PT ratios of 1.5-2 **x** control (INR ≈ 3-4) may be needed for recurrent systemic embolism, mechanical heart valves… (the recommended ranges for the **International Normalized Ratio (INR)** are shown in *Table 3-5*).

NB: Warfarin should not be started until a therapeutic PTT has been achieved on heparin to reduce the risk of “Coumadin necrosis.” During the first ≈ 3 days of warfarin therapy, patients are actually <u>hypercoagulable</u> (secondary to reduction of vitamin-K dependent anticoagulation factors protein C and protein S), therefore, continue heparin during the first few days.

Supplied: scored tabs of 1, 2, 2.5, 5, 7.5 and 10 mg. IV form: 5mg/vial.

Table 3-5 Recommended INRs[29]

Indication	INR
• mechanical prosthetic heart valve • prevention of recurrent MI	2.5-3.5
antiphospholipid antibody syndrome[30] (*see page 1025*)	≥ 3
all other indications (DVT prophylaxis and treatment, PE, atrial fibrillation, recurrent systemic embolism, tissue heart valves)	2-3

heparin DRUG INFO

Rx: administered as IV drip or sub-Q bolus. To anticoagulate average weight patient, give 5000 U bolus IV, follow with 1000 U/hr IV drip. Titrate to therapeutic anticoagulation of APTT = 2-2.5 **x** control (for DVT, some recommend 1.5-2 **x** control[31]).

Rx low-dose ("mini-dose") heparin: 5000 IU SQ q 8 or 12 hrs. Routine monitoring of APTT is usually not done, although occasionally patients may become fully anticoagulated on this regimen.

Side effects: (see *Anticoagulant considerations in neurosurgery* above): hemorrhage, thrombosis[32] (heparin activates anti-thrombin III and can cause platelet aggregation) which can result in MIs, CVAs, DVTs, PEs, etc. Heparin induced thrombocytopenia (HIT): transient mild thrombocytopenia is fairly common in the first few days after initiating heparin therapy, however severe thrombocytopenia occurs in 1-2% of patients receiving heparin > 4 days (usually has a delayed onset of 6-12 days, and is due to consumption in heparin-induced thrombosis or to antibodies formed against a heparin-platelet protein complex). The incidence of HIT in SAH is 5-6% and was similar with enoxaparin[33]. Consider use of lepirudin (*see below*) in thrombocytopenic patients. Chronic therapy may cause osteoporosis.

dabigatran (Pradaxa®) DRUG INFO

An oral anticoagulant in the class of direct thrombin inhibitors.

Administered as the prodrug dabigatran etexilate. Must be stopped 24 hrs prior to surgery.

LOW MOLECULAR WEIGHT HEPARINS[34, 35]

Low molecular weight heparins **(LMWH)** (average molecular weight = 3000-8000 daltons) are derived from unfractionated heparin (average MW = 12,000-15,000 daltons). LMWHs differ from unfractionated heparin because they have a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity which theoretically should produce anti-thrombic effects with fewer hemorrhagic complications. Realization of this benefit has been very minor in clinical trials. LMWH have greater bioavailability after sub-Q injection leading to more predictable plasma levels which eliminates the need to monitor biologic activity (such as APTT). LMWH have a longer half-life and therefore require fewer doses per day. LMWH have a lower incidence of thrombocytopenia. More effective in DVT prophylaxis than warfarin in orthopedic surgery[36].

Spinal epidural hematomas: There have been a number of case reports of spinal epidural hematomas occurring in patients on LMWH (primarily enoxaparin) who also underwent spinal/epidural anesthesia or lumbar puncture, primarily in elderly women undergoing orthopedic surgery. Some have had significant neurologic sequelae, including permanent paralysis[37]. The risk is further increased by the use of NSAIDs, platelet inhibitors, or other anticoagulants, and with traumatic or repeated epidural or spinal puncture.

Reversal of anticoagulation: Protamine sulfate may be used (*see page 41*).

Available low molecular weight heparins

Drugs include:

- enoxaparin (Lovenox®): *see below*
- dalteparin (Fragmin®): ***Rx*** 2500 anti-Xa U SQ q d
- ardeparin (Normiflo®): half-life = 3.3 hrs. ***Rx*** 50 anti-Xa U/kg SQ q 12 hrs
- danaparoid (Orgaran®): a heparinoid. Even higher anti-Xa:anti-IIa ratio than LMWHs. Does not require laboratory monitoring. ***Rx*** 750 anti-Xa U SQ BID
- tinzaparin (Logiparin®, Innohep®): not available in U.S. ***Rx*** 175 anti-Xa U per kg SQ once daily
- fondaparinux (Arixta®): *see below*

• lepirudin (Refludan®): *see below*
• bivalirudin: *see below*

enoxaparin (Lovenox®) DRUG INFO

Rx dosage established following hip replacement is 30 mg SQ BID **x** 7-14 days (alternative: 40 mg SQ q d). **Pharmacokinetics:** After SQ injection, peak serum concentration occurs in 3-5 hrs. Half-life: 4.5 hrs.

lepirudin (Refludan®) DRUG INFO

A direct thrombin inhibitor which blocks the thrombogenic activity of thrombin, and, unlike heparin, also acts on clot-bound thrombin. It is FDA approved for anticoagulation in patients with heparin-induced thrombocytopenia[38].

Rx: loading dose of 0.4 mg/kg (up to 44 mg) IV, followed by continuous infusion of 0.15 mg/kg/hr for 2-10 days. The dose is titrated to a target aPTT ratio of 1.5-2.5. **Supplied**: 1 ml vials containing 50 mg.

bivalirudin DRUG INFO

Directly inhibits thrombin and increases rapidity of plasminogen activator-mediated recanalization. No effective reversal.

Rx: IV loading dose of 0.5 mg/kg IV, followed by continuous infusion of 1.75 mg/kg/hr. Intraarterial: inject 15 mg in 10 ml of heparinized saline via a microcatheter.

Factor Xa inhibitors

fondaparinux (Arixtra®) DRUG INFO

A synthetic analog of the pentasaccharide binding sequence of heparin. Increases factor Xa inhibition without affecting factor IIa (thrombin)[39]. Unfractionated & LMW can cause immune-mediated heparin-induced thrombocytopenia **(HIT)**. Fondaparinux has not caused HIT. May be more

effective than enoxaparin (Lovenox®) for preventing postop DVTs. **SIDE EFFECTS:** Bleeding is the most common side effect (may be increased by concurrent NSAID use). ✖ Contraindicated with severe renal impairment.

Rx: 2.5 mg SQ injection q d. **SUPPLIED**: 2.5 mg single-dose syringes. **PHARMACOKINETICS:** Peak activity occurs in 2-3 hrs. Elimination: in urine. Half-life: 17-21 hrs.

3.2.2.2. Coagulopathies

CORRECTION OF COAGULOPATHIES OR REVERSAL OF ANTICOAGULANTS

For recommended normal values for coagulation studies in neurosurgery, *see page 37*.

Platelets

See page 34 for indications and administration guidelines.

Fresh frozen plasma

To reverse warfarin anticoagulation, use the following as a starting point and recheck PT/PTT afterwards:

- when patient is “therapeutically anticoagulated” start with 2-3 units FFP (approximately 15 ml/kg is usually needed)
- for severely prolonged PT/PTT, start with 6 units FFP

Prothrombin complex concentrate

Warfarin induced anticoagulation may be reversed up to 4 or 5 times more quickly with prothrombin complex concentrate **(PCC)** (contains coagulation factors II, IX, and X) than with FFP[40]. Patient may become hyperthrombotic with this.

vitamin K (Aquamephyton®) **DRUG INFO**

To reverse elevated PT from warfarin, give aqueous colloidal solution of vitamin K_1 (phytonadione, Aquamephyton®). Doses > 10 mg may produce warfarin resistance for up to 1 week. FFP may be administered concurrently for more rapid correction (*see above*). For recommended levels of PT, *see*

page 37.

***Rx* adult**: start with 10-15 mg IM; the effect takes 6-12 hrs (in absence of liver disease). Repeat dose if needed. The average total dose needed to reverse therapeutic anticoagulation is 25-35 mg.

IV administration has been associated with severe reactions (possibly anaphylactic), including hypotension and even fatalities (even with proper precautions to dilute and administer slowly), therefore IV route is reserved only for situations where other routes are not feasible and the serious risk is justified. ***Rx* IV** (when IM route not feasible): 10-20 mg IV at a rate of injection not to exceed 1 mg/min (e.g. put 10 mg in 50 ml of D5W and give over 30 minutes).

protamine sulfate DRUG INFO

For **heparin**: 1 mg protamine reverses ≈ 100 U heparin (give slowly, not to exceed 50 mg in any 10 min period). Therapy should be guided by coagulation studies.

Low molecular weight heparins (LMWH): slow IV injection of a 1% solution of protamine can also be used to reverse LMWHs as follows:

Enoxaparin (Lovenox®): ≈ 60% of Lovenox can be reversed with 1mg of protamine for every mg of Lovenox given (maximum dose = 50 mg) within the last 8 hrs, and 0.5 mg of protamine for every mg of Lovenox given from 8-12 hrs prior. Protamine is probably not needed for Lovenox given > 12 hrs earlier.

Dalteparin (Fragmin®) or **ardeparin** (Normiflo®): 1 mg of protamine for every 100 anti-Xa IU of the LMWH (maximum dose = 50 mg) with a second infusion of 0.5 mg protamine for every 100 anti-Xa IU of LMWH if the APTT remains elevated 2-4 hours after the first dose is completed.

Danaparoid and Hirudin: no known reversing agent.

desmopressin (DDAVP®) DRUG INFO

Causes an increase in factor III coagulant activity and von Willebrand factor which helps coagulation and platelet activity in hemophilia A and in von Willebrand's disease Type I (where the factors are normal in makeup but low in concentration, ✖ but may cause thrombocytopenia in von Willebrand's disease Type IIB where factors may be ab-normal or missing).

Rx 0.3 mcg/kg (use 50 ml of diluent for doses $\leq$ 3 mcg, use 10 ml for doses > 3 mcg) given over 15-30 minutes 30 minutes prior to a surgical procedure.

Elevated pre-op PTT

In a patient with no history of coagulopathy, a significantly elevated pre-op PTT is commonly due to either a factor deficiency or to lupus anticoagulant. Work-up:

1. mixing study
2. lupus coagulant

If the mixing study corrects the elevated PTT, then there is probably a factor deficiency. Consult a hematologist.

Lupus anticoagulant: If the test for lupus anticoagulant is positive, then the major risk to the patient with surgery is not bleeding, rather it is thromboembolism. Management recommendations:

1. as soon as feasible post-op, start patient on heparin (*see page 39*) or LMW heparin (*see page 39*), e.g. Lovenox
2. at the same time start warfarin, and maintain therapeutic anticoagulation for 3-4 weeks (the risk of DVT/PE is actually highest in the first few weeks post-op)
3. mobilize as soon as possible post-op
4. consider vena-cava interruption filter in patients for whom anticoagulation is contraindicated

THROMBOEMBOLISM IN NEUROSURGERY

Deep-vein thrombosis (DVT) is of concern primarily because of the potential for material (clot, platelet clumps…) to dislodge and form emboli (including pulmonary emboli, **(PE)**) which may cause pulmonary infarction, sudden death (from cardiac arrest), or cerebral infarction (from a paradoxical embolus, which may occur in the presence of a patent foramen ovale, see *Cardiogenic brain embolism*, page 1022). The reported mortality from DVT in the LEs ranges from 9-50%[41]. DVT limited to the calf has a low threat (< 1%) of embolization, however, these clots later extend into the proximal deep veins in 30-50% of cases[41], from where embolization may occur (in 40-50%), or they may produce postphlebitic syndrome.

Neurosurgical patients are particularly prone to developing DVTs (estimated risk: 19-50%) due at least in part to the relatively high frequency of the following:

1. long operating times of some procedures
2. prolonged bed rest pre- and/or post-op
3. paralyzed limbs (e.g. in spinal cord injuries or stroke patients)
4. alterations in coagulation status
   A. in patients with brain tumors (*see below*) or head injury[42]
      1. related to the condition itself
      2. due to release of brain thromboplastins during brain surgery
   B. increased blood viscosity with concomitant "sludging"
      1. from dehydration therapy sometimes used to reduce cerebral edema
      2. from volume loss following SAH (cerebral salt wasting)
   C. use of high-dose glucocorticoids

Specific "neurological" risk factors for DVT and PE include[41]:

1. spinal cord injury (*see* *page 937*)
2. brain tumor: autopsy prevalence of DVT = 28%, of PE = 8.4%. Incidence using 125Ifibrinogen[43]: meningioma 72%, malignant glioma 60%, metastasis 20%. Risk may be reduced by pre-op use of aspirin[44]
3. subarachnoid hemorrhage
4. head trauma: especially severe TBI (*see* *page 907*)
5. stroke: incidence of PE = 1-19.8%, with mortality of 25-100%
6. neurosurgical operation: risk is higher following craniotomy for supratentorial tumors (7% of 492 patients) than p-fossa tumors (0 out of 141)[45]

Prophylaxis against DVT

Options include:

1. general measures
   A. passive range of motion
   B. ambulate appropriate patients as early as possible
2. mechanical techniques (minimal risk of complications):
   A. pneumatic compression boots[46] **(PCBs)** or sequential compression devices **(SCDs)**: reduces the incidence of DVTs and probably PEs. Do not use if DVTs already present. Continue use until patient able to

walk 3-4 hrs per day

B. TED Stockings®[A]: **(TEDS)** applies graduated pressure, higher distally. As effective as PCB. No evidence that the benefit is additive[41]. Care should be taken to avoid a tourniquet effect at the proximal end

C. electrical stimulation of calf muscles

D. rotating beds

3. anticoagulation[B]

A. full anticoagulation is associated with perioperative complications[47]

B. "low-dose" anticoagulation[48] (low-dose heparin): 5000 IU SQ q 8 or 12 hrs, starting 2 hrs pre-op or on admission to hospital. Potential for hazardous hemorrhage within brain or spinal canal has limited its use

C. low molecular weight heparins and heparinoids (*see page 39*): not a homogeneous group. Efficacy in neurosurgical prophylaxis has not been determined

D. aspirin: role in DVT prophylaxis is limited because ASA inhibits platelet aggregation, and platelets play only a minor role in DVT

4. combination of PCBs and "mini-dose" heparin starting on the morning of post-op day 1 (with no evidence of significant complications)[49]

A. TEDS® is a registered trademark. "TED" stands for thromboembolic disease

B. for contraindications and considerations of anticoagulation in neurosurgery, *see page 36*

Recommendations

Recommended prophylaxis varies with the risk of developing DVT, as illustrated in *Table 3-6*[41]. Also *see page 937* for details of prophylaxis in cervical spinal cord injuries.

Diagnosis of DVT

The clinical diagnosis of DVT is very unreliable. A patient with the "classic signs" of a hot, swollen, and tender calf, or a positive Homans' sign (calf pain on dorsiflexion of the ankle) will have a DVT only 20-50% of the time[41]. 50-60% of patients with DVT will not have these findings.

Table 3-6 Risk & prophylaxis of DVT in neurosurgical patients*

Risk group	Estimated risk of calf DVT	Typical neurosurgical patients	Treatment recommendation
low risk	< 10%	age < 40 yrs, minimal general risk factors, surgery with < 30 minutes general anesthesia	no prophylaxis, or PCB/TEDS
moderate risk	10-40%	age ≥ 40 yrs, malignancy, prolonged bed rest, extensive surgery, varicose veins, obesity, surgery > 30 minutes duration (except simple lumbar discectomy), SAH, head injury	PCB/TEDs; or for patients without ICH or SAH, minidose heparin
high risk	40-80%	history of DVT or PE, paralysis† (para- or quadriplegia or hemiparesis), brain tumor (especially meningioma or malignant glioma)	PCB/TEDS + (in patients without ICH or SAH) minidose heparin

* abbreviations: DVT = deep venous thrombosis, PCB = pneumatic compression device, TEDS = TED (thromboembolic disease) Stockings®, ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage

† *see page 937* for specifics regarding DVT prophylaxis in cervical SCI

Laboratory tests

- contrast venography: the "gold standard", however it is invasive and carries risk of iodine reaction, occasionally produces phlebitis, not readily repeated
- Doppler ultrasound with B-mode imaging: 95% sensitive and 99% specific for proximal DVT. Less effective for calf DVT[50]. May be used in immobilized or casted LE (unlike IPG). Widely accepted as the non-invasive test of choice for DVT[51]
- impedance plethysmography **(IPG)**: looks for reduced electrical impedance produced by blood flow from the calf following relaxation of a pneumatic tourniquet. Good in detecting proximal DVT, not sensitive for calf DVT. A positive study indicates DVT that should be treated, a negative study can occur with non-occlusive DVT or with good collaterals, and should be repeated over a 2 week period
- 125I-fibrinogen: radiolabeled fibrinogen is incorporated into the developing thrombus. Better for calf DVT than proximal DVT. Expensive, and many false positives. Risk of HIV transmission has resulted in withdrawal of use
- **D-dimer** (a specific fibrin degradation product): high levels are associated with DVT and PE[52]

Treatment of DVT

1. bed rest, with elevation of involved leg(s)
2. unless anticoagulation is contraindicated (*see page 36*), start heparin (as outlined in *Anticoagulation* on page 36, aim for APTT = 1.5-2 **x** control) or fixed dose of LMW heparinoids (e.g. tinzaparin (Logiparin®[53], or in the U.S. enoxaparin (Lovenox®) *see page 40*): simultaneously initiate warfarin therapy. Heparin can be stopped after ≈ 5 days[54]
3. in patients where anticoagulation is contraindicated, consider inferior vena cava interruption or placement of a filter (e.g. Greenfield filter)
4. in non-paralyzed patients, cautiously begin to ambulate after ≈ 7-10 days
5. wear anti-embolic stocking on affected LE indefinitely (limb is always at risk of recurrent DVT)

3.2.3. Extramedullary hematopoiesis

In chronic anemias (especially thalassemia major, AKA Cooley's anemia), low hematocrit results in chronic over-stimulation of bone marrow to produce RBCs. This results in systemic bony abnormalities, cardiomyopathy (due to hemochromatosis caused by increased breakdown of defective RBCs).

Pertinent to the CNS, there are three sites where extramedullary hematopoiesis **(EMH)** can cause findings:

- skull: produces "hair-on-end" appearance on skull x-ray
- vertebral bodies: may result in epidural cord compression[55] (*see below*)
- choroid plexus

Epidural cord compression from EMH

The exuberant tissue is very radiosensitive, however, the patient may be somewhat dependent on the hematopoietic capacity of the tissue.

Treatment

Surgical excision followed by radiation therapy has been the recommended treatment. Repeated blood transfusions may help reduce EMH and may be useful post-op instead of RTX except for refractory cases[55].

Surgery on these patients is difficult because of:

1. low platelet count
2. poor condition of bone

3. cardiomyopathy: increased anesthetic risk
4. anemia, coupled with the fact that most of these patients are "iron-toxic" from multiple previous transfusions
5. total removal of the mass is not always possible

3.3. Pharmacology

3.3.1. Analgesics

For a discussion of types of pain and pain procedures, *see page 548*.

GENERAL PRINCIPLES

The key to good pain control is the early use of adequate levels of effective analgesics. For cancer pain, scheduled dosing is superior to PRN dosing, and "rescue" medication should be available[56]. Nonopioid analgesics should be continued as more potent medications and invasive techniques are utilized.

ANALGESICS FOR SOME SPECIFIC TYPES OF PAIN

Visceral or deafferentation pain

May sometimes be effectively treated with tricyclic antidepressants (*see page 50*) or with anticonvulsant class drugs (gabapentin or pregabalin - *see page 50*).

Tryptophan may be effective (*see page 50*).

Carbamazepine (Tegretol®) may be useful for paroxysmal, lancinating pain.

Pain from metastatic bone disease

Steroids, aspirin, or NSAIDs are especially helpful, probably by reducing prostaglandin mediated sensitization of A-delta and C fibers, and therefore may be preferred to acetaminophen.

3.3.1.1. Nonopioid analgesics

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

The anti-inflammatory properties of NSAIDs is primarily due to inhibition of the enzyme cyclooxygenase **(COX)** which participates in the synthesis of prostaglandins and thromboxanes[57].

Characteristics of nonselective nonsteroidal anti-inflammatory drugs:

- all are given orally except ketorolac tromethamine (Toradol®) (*see below*)
- no dependence develops
- additive effect improves the pain relief with opioid analgesics
- NSAIDs (and APAP) demonstrate a **ceiling effect**: a maximum dose above which no further analgesia is obtained. For aspirin and APAP, this is usually between 650-1300 mg, and is often higher for other NSAIDs which may also have a longer duration of action
- risk of GI upset is common, more serious risks of hepatotoxicity[58], or GI ulceration, hemorrhage, or perforation are less common
- taking medication with meals or antacids has not been proven effective in reducing GI side effects. **Misoprostol** (Cytotec®), a prostaglandin, may be effective in mitigating NSAID-induced gastric erosion or peptic ulcer. Contraindicated in pregnancy. ***Rx*** 200 mcg PO QID with food as long as patient is on NSAIDs. If not tolerated, use 100 mcg. ✖ CAUTION: an abortifacient. Should not be given to pregnant women or women of childbearing potential
- most reversibly inhibit platelet function and prolong bleeding time (nonacetlyated salicylates have less antiplatelet action, e.g. salsalate, trisalicylate, nabumetome). Aspirin, unlike all other NSAIDS, irreversibly binds to cyclooxygenase and thus inhibits platelet function for the 8-10 day life of the platelet
- all cause sodium and water retention and carry the risk of NSAID-induced nephrotoxicity[59] (renal insufficiency, interstitial nephritis, nephrotic syndrome, hyperkalemia)

Table 3-7 Nonsteroidal anti-inflammatory drugs (NSAIDs)

Generic name	Proprietary (®)	Typical adult oral dose*	Tabs/caps availability (mg)†	Daily maximum (mg)
aspirin‡	(many)	500-1000 mg PO q 4-6 hrs (ceiling dose ≈ 1 gm)	325, 500	4000
bromfenac[60]	Duract	25 mg PO q 6-8 hrs on empty stomach up to 10 d	25	150
diclofenac	Voltaren, Cataflam	start at 25 mg QID; additional dose q hs PRN; increase up to 50 mg TID or QID, or 75 mg BID	25, 50, 75	200
diflunisol	Dolobid	1000 mg initial; then 500 mg BID	250, 500	1500
etodolac	Lodine	for acute pain: 200-400 mg q 6-8 hrs	200, 300 caps, 400 tabs	1200
fenoprofen	Nalfon	200 mg q 4-6 hrs; for rheumatoid arthritis 300-600 mg TID-QID	200, 300, 600	3200
flurbiprofen	Ansaid	50 mg TID-QID or 100 mg TID	50, 100	300
ketoprofen	Orudis	start at 75 mg TID or 50 mg QID, ↑to 150-300 mg daily DIV TID-QID	25, 50, 75	300
	Oruvail	extended release capsule 150 mg q d	ER† 150	
ketorolac	Toradol	*see below*	*see below*	
ibuprofen§	Motrin	400-800 mg QID (ceiling dose: 800 mg)	300, 400, 600, 800	3200
indomethacin	Indocin	25 mg TID, ↑ by 25 mg total per day PRN	25, 50, SR 75	150-200
meclofenamate	Meclomen	50 mg q 4-6 hrs; ↑ to 100 mg QID if needed	50, 100	400
mefenamic	Ponstel	500 mg initial; then 250 mg q 6 hrs	250	
nabumetomeΔ	Relafen	1000-2000 mg/d given in 1 or 2 doses	500, 750	2000
naproxen	Naprosyn	500 mg, then 250 mg q 6-8 hrs	250, 375, 500	<1250
naproxen sodium	Anaprox	550 mg, followed by 275 mg q 6-8 hrs	275, DS = 550	1375
oxaprozin	Daypro	1200 mg q d (1st day may take 1800)	600	1800
phenylbutazone	Butazolidin	high incidence of agranulocytosis. Not first DOC, and not a simple analgesic		
piroxicam	Feldene	10-20 mg q d (steady state takes 7-12 d)	10, 20	
sulindac	Clinoril	200 mg BID; ↓ to 150 BID when pain controlled	150, 200	400
salsalate	Disalcid	3000 mg divided BID-TID (e.g. 500 mg 2-tabs TID)	500, 750	
tolmetin	Tolectin	400 mg TID (bioavailability is reduced by food)	200, DS = 400, 600	1800
trisalicylate	Trilisate	2000-3000 mg/d usually divided BID (but may be divided TID)	500, 750, 1000, liquid 500mg/5ml	

* when dosage ranges are given, use the smallest effective dose

† abbreviations: DS = double strength; SR = slow release; ER = extended release; DOC = drug of choice

‡ aspirin: has unique effectiveness in pain from bone metastases

§ ibuprofen: is available as a suspension (PediaProfen®) 100 mg/ml; dose for children 6 mos to 12 yrs age is 5-10 mg/kg with a maximum of 40 mg/kg/day (not FDA approved for children because of possible Reye's syndrome)

Δ unlike most NSAIDs, nabumetome does not interfere with platelet function

ketorolac tromethamine (Toradol®) DRUG INFO

The only parenteral NSAID approved for use in pain control in the U.S. Analgesic effect is more potent than anti-inflammatory effect. Half-life ≈ 6 hrs. May be useful to control pain in the following situations:

1. where the avoidance of sedation or respiratory depression is critical

2. when constipation cannot be tolerated
3. for patients who are nauseated by narcotics
4. where narcotic dependency is a serious concern
5. when epidural morphine has been used and further analgesia is needed without risk of respiratory depression (agonist type narcotics are contraindicated)
6. cautions:
   A. not indicated for use > 72 hrs (complications have been reported primarily with prolonged use of the oral form)
   B. use with caution in postoperative patients since (as with most NSAIDs) bleeding time is prolonged by platelet function inhibition (risk of GI or opsite hemorrhage is small, but is increased in patients > 75 yrs old, when used > 5 days, and when used in higher doses[61])
   C. even though IM dosing circumvents the GI system, gastric mucosal irritation and erosions may occur as with all NSAIDs (avoid use with PUD)
   D. as with all NSAIDs, use with caution in patients at risk for renal side effects

***Rx* Parenteral:** For single dose administration: 30 mg IV or 60 mg IM in healthy adult. For multiple dosing: 30 mg IV or IM q 6 hrs PRN. Maximum dosage: 120 mg/day. Parenteral use should not exceed 5 days (3 days may be a better guideline).

For patient weight < 50 kg, age > 65 yrs, or reduced renal function (creatinine clearance < 50 ml/min), all of the above dosages are halved (max daily dose: 60 mg). Creatinine clearance can be estimated using the Cockcroft-Gault equation[62] (*Eq 3-1*), with normal values ≥ 60 ml/min.

$$\text{Creatinine clearance (ml/min)} = \frac{[140 - \text{age (years)}] \times \text{ideal wt (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times (0.85 \text{ for females}) \qquad \textbf{Eq 3-1}$$

***Rx* PO:** Indicated only as a continuation of IV or IM therapy, not for routine use as an NSAID. Switching from IM to PO: start with 10 mg PO q 4-6 hrs (combined PO and IM dose should be ≤ 120 mg on the day of transition). **SUPPLIED**: 10 mg tablets.

ACETAMINOPHEN

Table 3-8 Acetaminophen dosing

Medication	Dosage
acetaminophen **(APAP)** (Tylenol®)	adult dose: 650 or 1000 mg PO/PR q 4-6 hrs, not to exceed 4000 mg/day* lpediatric dose: infants: 10-15 mg/kg PO/PR q 4-6 hrs children: 1 grain/yr age (= 65 mg/yr up to 650 mg) PO/PR q 4-6 hrs not to exceed 15 mg/kg q 4 hrs

* hepatic toxicity from APAP: usually with doses ≥ 10 gm/day, rare at doses < 4000 mg. However, may occur at lower doses (even at high therapeutic doses) in alcoholics, fasting patients, and those taking cytochrome P-450 enzyme-inducing drugs

3.3.1.2. Opioid analgesics

Narcotics are most commonly used for moderate to severe acute pain or cancer pain (some experts characterize cancer pain as recurrent acute pain and not chronic pain).

Characteristics of narcotics:

- <u>no</u> **ceiling effect** (*see page 45*): i.e. increasing dosage increases the effectiveness (although with weak opioids for moderate pain, side effects may limit dosages to relatively low levels[56])
- with chronic use, tolerance develops (physical and psychological)
- overdose possible, with the potential for respiratory depression with all, and seizures with some (*see page 275*)

MILD TO MODERATE PAIN

Some useful medications are shown in *Table 3-9*.

Table 3-9 Weak opioids for mild to moderate pain

Medication	Dosage
codeine	usual adult dose: 30-60 mg IM/PO q 3 hrs PRN; use with caution in nursing mothers (30 mg PO is equivalent to 300 mg aspirin) pediatric dose: 0.5-1 mg/kg/dose q 4-6 hrs PO or IV PRN
propoxyphene (Darvon®…)	usually used as propoxyphene napsylate with acetaminophen (Darvocet-N)* Darvocet-N 100 ***Rx***: 1-2 PO q 4-6 hrs PRN
pentazocine (Talwin®, Talwin® Nx, Talacen®)	pentazocine is a mixed agonist-antagonist
	→ 12.5 mg pentazocine, 325 mg ASA. ***Rx***: 2 PO TID-QID PRN
	→ 50 mg pentazocine, 0.5 mg naloxone. ***Rx***: 1-2 PO q 3-4 hrs PRN up to 12 tabs/day

	→ 25 mg pentazocine, 650 mg APAP. ***Rx***: 1 PO q 4-6 hrs PRN up to 6 tabs/day
tramadol (Ultram®)	(*see below*)

* *CAUTION: propoxyphene can cause dangerous elevations of carbamazepine levels*

Codeine and its congeners, propoxyphene and pentazocine, are usually no more effective that ASA or APAP and are usually combined with these drugs.

tramadol (Ultram®) DRUG INFO

An oral opioid agonist that binds to μ-opioid receptors, and is also a centrally acting analgesic that inhibits reuptake of norepinephrine and serotonin. For acute pain, 100 mg is comparable to codeine 60 mg with ASA or APAP[63, 64]. There has been no report of respiratory depression when oral dosing recommendations are followed. Seizures and opioid-like dependence have been reported[64].

Rx 50 to 100 mg PO q 4-6 hrs PRN pain up to a maximum of 400 mg/day (or 300 mg/d for older patients). For moderately severe acute pain, an initial dose of 100 mg followed by 50 mg doses may suffice. **SUPPLIED**: 50 mg tabs.

MODERATE TO SEVERE PAIN

Table 3-10 Opioids for moderate to severe pain

Medication	Dosage
hydrocodone	(Vicodin®, Lorcet®, Lortab®...): 5 mg hydrocodone + 500 mg acetaminophen; (Vicodin ES®, Lortab 7.5/500®): 7.5 mg hydrocodone + 500 mg APAP; ***Rx*** 1 PO q 6 hrs PRN (may increase up to 2 tabs PO q 3-4 hrs not to exceed 8 pills/24 hrs).
	(Lorcet® Plus, Lorcet® 10/650): 7.5 or 10 mg hydrocodone (respectively) + 650 mg APAP; ***Rx*** 1 tab PO q 6 hrs PRN (not to exceed 6 tabs in 24 hrs).
	(Lortab® 10/500: 10 mg. hydrocodone + 500 mg APAP); ***Rx***: 1-2 PO q 4 hrs PRN up to 6 tabs/day.
	(Norco®): 10 mg hydrocodone + 325 mg APAP scored tabs; ***Rx***: 1 PO q 4 hrs PRN up to 6 tabs/day.
hydromorphone	Dilaudid®: (*see Table 3-11*)
morphine	used in low doses (*see Table 3-11*)
levorphanol	Levo-Dromoran®: 2 mg IM ≈ 10 mg morphine; long half-life (*see Table 3-11*)

oxycodone	**Supplied**: usually available in combination as: aspirin 325 mg with oxycodone 5 mg (Percodan®) or acetaminophen (APAP) (Tylox® = APAP 500 mg + oxycodone 5 mg) (Percocet® = oxycodone/APAP in 2.5/325, 5/325, 7.5/500, 10/650) dose: 1 PO q 3-4 hrs PRN (may increase up to 2 PO q 3 hrs*) **Supplied**: also available alone as **OxyIR**® 5 mg, OxyFast® oral solution of 20 mg/ml, or in controlled-release tablets as **OxyContin**® 10, 20, 40, 80† & 160† mg (which last 12 hours, achieving steady state in 24-36 hours). ***Rx*** Adult: OxyContin® tablets are taken whole and are not to be divided, chewed or crushed. It is intended for management of moderate to severe pain when continuous around-the-clock analgesic is needed for an extended period of time and is not intended for use as a PRN analgesic. For opiate naive patients, start with 10 mg PO q 12 hrs. For patients on narcotic medications, a conversion table is provided below for some medications. Titrate dose every 1-2 days, increasing dose by 25-50% q 12 hrs.

Conversion table for starting OxyContin®

Preparation currently being used	Dose	Suggested starting dose of OxyContin®
oxycodone combination pills (Tylox, Percodan…) or Lortab, Vicodin or Tylenol #3	1-5 pills/day	10-20 mg PO q 12 hrs
	6-9 pills/day	20-30 mg PO q 12 hrs
	10-12 pills/day	30-40 mg PO q 12 hrs
IV PCA morphine	determine total MSO4 dose used per 24 hrs	multiply total MSO4 dose in 24 hrs X 1.3 for total OxyContin dose in 24 hrs

* not to exceed 4000 mg of acetaminophen/24 hrs (see footnote to *Table 3-8* on *page 46*)

† for use only in opioid-tolerant patients

Severe pain

Table 3-11 Equianalgesic doses for SEVERE pain, AGONIST opioids*

Drug name: generic (proprietary®)	Route	Dose (mg)	Peak (hrs)	Duration (hrs)	Comments
morphine	IM	10	0.5-1	4-6	respiratory depression
	PO	20-60†	1.5-2	4-7	long acting PO forms: MS Contin®, Avinza® (*see below*)
codeine (not recommended at these doses)	IM	130		3-5	these high doses cause unacceptable side effects
	PO	200			
meperidine‡ (Demerol®)	IM	75	0.5-1	4-5	avoid prolonged use‡, irritating to tissues
	PO	300-400	1-2	4-6	
methadone§ (Dolophine®)	IM	10	0.5-1	4-6	long half-life§
	PO	20	1.5-2	4-7	
levorphanol§ (Levo-Dromoran®)	IM	1.5-2.5		4-6	long half-life§
	PO	2-4			
oxycodone	IM	15			
(e.g. Tylox®Δ)	PO	30	1	3-4	combination (Tylox®) or liquid
(OxyContin®)	PO	30-40		12	*see Table 3-10*
oxymorphone (Numorphan®)	IM	1		3-5	available as suppository
	PR	10			
hydromorphone (Dilaudid®)	IM	1.5	0.5-1	3-4	
	PO	7.5	1.5-2	3-4	supplied: 1, 2, 3, & 4 mg tabs
fentanyl (Sublimaze®)	IV	0.1		1-2	not recommended for acute pain control, esp. in narcotic naive pts.
transdermal fentanyl patch (Duragesic®)¶	transdermal	**	12-24	72	patches of 25, 50, 75, 100 or 125 mcg/hr (use lowest effective)

* parenteral route is referenced to 10 mg IM morphine

† IM:PO potency ratio for morphine is 1:6 for single doses, but changes to 1:2-3 with chronic dosing

‡ high doses or long-term use is not recommended because meperidine is metabolized to nor-meperidine, a stimulant with a 15-20 hour half-life, that may accumulate and cause agitation or other CNS hyperactivity (including delerium and seizures), may also manifest when given agonist/antagonist drugs. Meperidine may also cause severe encephalopathy and death when given with MAOIs

§ due to long half-life, repeated dosing can lead to accumulation and CNS depression (must reduce dose after ≈ 3 days, even though the analgesic half-life does not change), especially in the elderly or debilitated patient. Use should be limited to physicians with experience using these drugs

Δ may not be practical for use in severe pain since 1 Tylox® contains only 5 mg oxycodone (the acetaminophen limits the dosage), may use OxyContin® for higher doses of oxycodone

¶ ✖ should not be used as routine post-op analgesic (risk of respiratory depression). Apply 1 patch to upper torso, replace q 72 hrs PRN.

** conversion from total daily parenteral morphine as follows:

8-27 mg MSO4/day	Duragesic 25 mcg/hr
28-37 mg MSO4/day	Duragesic 50 mcg/hr
38-52 mg MSO4/day	Duragesic 75 mcg/hr
53-67 mg MSO4/day	Duragesic 100 mcg/hr
68-82 mg MSO4/day	Duragesic 125 mcg/hr

Avinza® (extended release morphine) DRUG INFO

Once daily oral morphine formulation using a spherical oral drug absorption system **(SODAS)** (numerous ammonio-methacrylate copolymer

beads, ≈ 1 mm dia.).

Rx: Dosage is titrated based on patient's opioid tolerance and degree of pain. Taken as 1 capsule p.o. q d. Not to be taken "PRN". Not for post-op pain. ✖ CAUTION: To prevent potentially fatal doses of morphine, capsules are to be swallowed whole, and are not to be chewed, crushed or dissolved. However, the contents of the capsule (the beads) may be sprinkled on applesauce for those unable to swallow the capsules, but the beads are not to be chewed or crushed. **Side effects:** Due to the potentially nephrotoxic effect of fumaric acid used in SODAS, the maximum dose of Avinza is 1600 mg/d. Doses ≥ 60 mg are for opioid tolerant patients only. **Supplied**: 30, 60, 90 & 120 mg capsules.

Palladone® (extended release hydromorphone) DRUG INFO

Once daily extended release hydromorphone HCl (immediate release forms include Dilaudid®), a semisynthetic congener of morphine and active metabolite of hydrocodone. Risk for abuse or accidental overdosage by violating capsule or concurrent use of alcohol. Recommended only for opioid tolerant patients who have failed other therapies[65].

Rx A schedule II drug. For opioid tolerant patients only, start with 12-32 mg PO q 24 hours. Titrate upward by 25-50% increments every 2-3 days PRN. ✖ Capsules are not to be opened, broken, chewed, dissolved or crushed or taken with alcohol. Do not use if severe hepatic insufficiency. **Supplied**: 12, 16, 24 & 32 mg capsules.

Table 3-12 Equianalgesic doses for SEVERE pain, AGONIST/ANTAGONIST opioids (referenced to 10 mg IM morphine)

Drug name: generic (proprietary®)	Route	Dose (mg)	Peak (hrs)	Duration (hrs)	Comments
buprenorphine (Buprenex®)	IM	0.4			partial agonist
	SL	0.3			
MIXED AGONIST/ANTAGONIST*					
butorphanol (Stadol®)	IM	2	0.5-1	4-6	
nalbuphine (Nubain®)	IM	10	1	3-6	no sigma receptor occupation†
	IV	140 mcg/kg	0.5	2-5	
pentazocine (Talwin®‡)	IM†	20-40	0.5-1	4-6	
	PO†	180 (start @ 50)	1.5-2	4-7	
dezocine (Dalgan®)	IM	10		3-6	

* all can precipitate withdrawal symptoms in patients physically dependent on agonists

† most agonist/antagonist drugs occupy sigma receptors (Stadol > Nubain), which may cause hallucinations

‡ Talwin injectable (for IM use) contains only pentazocine. Talwin® Compound tablets contain ASA, ∴ for high PO doses, use Talwin Nx which contains no ASA (see *Table 3-9*, page 47)

3.3.1.3. Adjuvant pain medications

The following may have efficacy in enhancing the effectiveness of opioid analgesics (and thereby may reduce the required dose).

Tricyclic antidepressants: *see page 548*.

Tryptophan: an amino acid and a precursor of serotonin, may work by increasing serotonin levels. Requires high doses and has hypnotic effects, therefore 1.5-2 gm given usually q hs. Must give daily MVI as chronic tryptophan therapy depletes vitamin B_6.

Antihistamines: histamines play a role in nociception. Antihistamines, which are also anxiolytic, antiemetic, and mildly hypnotic, are effective as analgesics or as adjuvants. Hydroxyzine (Atarax®, Vistaril®): ***Rx*** start with 50 mg PO q AM and 100 mg PO q hs. May increase up to ≈ 200 mg daily.

Anticonvulsant-class drugs: carbamazepine, clonazepam, phenytoin, gabapentin or pregabalin tend to be more effective in *neuropathic* pain, e.g. from diabetic neuropathy, trigeminal neuralgia, post-herpetic neuralgia, glossopharyngeal neuralgia, and neuralgias due to nerve injury or infiltration with cancer[64]. See index for entries.

Phenothiazines: some cause mild reduction in nociception. Most are tranquilizing and antiemetic. Best known for this use is fluphenazine

(Prolixin®), usually given with a tricyclic antidepressant for neuropathic pain, see *Diabetic neuropathy*, *Treatment* on page 797. Phenothiazines may reduce the seizure threshold.

Corticosteroids: in addition to the reduction of toxic effects of radiation or chemo-therapy, they may potentiate narcotic analgesics. There are also a number of nonspecific beneficial effects: increased appetite, sense of well being, antiemetic. Side effects may limit usefulness (see *Possible deleterious side effects of steroids*, page 33).

Caffeine: although it possesses no intrinsic analgesic properties, doses of 65-200 mg enhance the analgesic effect of APAP, ASA or ibuprofen in for pain including: H/A, oral surgery pain and post-partum pain.

3.3.2. Antispasmodics/muscle relaxants for LBP

chlorpromazine (Thorazine®) **DRUG INFO**

Oral centrally-acting muscle relaxants have a sedating effect on the central nervous system, and there is little evidence of any other beneficial effect. Efficacy of use in patients with acute low back problems is dubious[66] (*see page 438*). Only doses are listed below. Be familiar with approved indications and precautions. For agents used for clinically significant spasticity, *see page 537*.

cyclobenzaprine (Flexeril®) **DRUG INFO**

Rx Adult: 10 mg PO TID-QID, usually not to exceed 2-3 weeks.

methocarbamol (Robaxin®) **DRUG INFO**

Robaxisal® is a combination of methocarbamol 400 mg + ASA 325 mg.

Rx Adult oral dose: initial dose with 500 mg tabs: 3 tabs PO QID **x** 48-72 hrs, and then 2 tabs PO QID. With 750 mg tabs: 2 tabs PO QID **x** 48-72 hrs, and then 1 tab PO q 4 hrs or 2 tabs PO TID. With Robaxisal®: for severe spasm/pain start at 3 tabs QID if patient can tolerate the ASA, then drop down

to maintenance dose of 2 tabs QID.

Rx Adult IV methocarbamol: 750 mg IVPB q 6-8 hrs for severe spasms.

Supplied: Injectable 1 g in 10 ml. Oral: 500 mg tablet. Robaxin®–750 has 750 mg methocarbamol.

✖ chlorzoxazone (Parafon Forte® DSC) DRUG INFO

Due to risk of serious and possibly fatal hepatotoxicity and questionable effectiveness as a muscle relaxant, there is little indication to use this drug[67].

diazepam (Valium®) DRUG INFO

Rx Adult dose for muscle spasms: 2-10 mg PO TID-QID. Also *see page 537* for more information and for use in spasticity.

carisoprodol (Soma®) DRUG INFO

Caution: not a true muscle relaxant (more of a sedative). May produce euphoria with resulting potential for abuse.

Rx Adult: 350 mg PO TID and q hs.

Supplied: 250 & 350 mg tablets.

quinine sulfate DRUG INFO

For "night cramps". Over 70% of people > 65 yrs old experience nocturnal cramps at some time (usually in the legs, sometimes in the hands). No well-controlled trials to document effectiveness. Meta-analysis suggested that the frequency of cramps can be reduced by ≈ 25% over 2 weeks of treatment, and by more over 4 weeks, but there was no change in severity or duration[68]. Avoid in pregnancy (abortifacient). Caution: even low dose can cause TTP in sensitive patients, repeated doses can cause cinchoism (watch for tinnitus, H/A, N/V, hearing loss) 69. Rule-out uremic neuropathy before treating (*see page 800*).

Rx Adult: 200 or 300 mg PO q hs PRN (better efficacy seen with regular dosing).

3.3.3. Benzodiazepines

Also see *Sedatives & paralytics*, page 23. All are effective for treating anxiety and insomnia, and vary only in pharmacokinetics or site of metabolism. Those with shorter duration of action are less likely to sedate, but are more prone to cause rebound depression or withdrawal syndrome (may include tachycardia, HTN, tremulousness, diaphoresis, dysphoria, confusion, muscle twitching, and seizures) upon discontinuation. Those with long duration of action are more likely to result in cumulative sedation, and impairment of psychomotor and intellectual function[70]. Lower doses are used for elderly patients. May be reversed with flumazenil (*see below*).

Side effects: ventilatory depression and hypotension exacerbated by opioids, worse in patients with COPD. All contraindicated in first trimester of pregnancy (cause congenital malformations)[71].

alprazolam (Xanax®) DRUG INFO

May have antidepressant effects similar to tricyclics, with more rapid onset.

Rx Adult: start at 0.25-0.5 mg PO TID, titrate to max of 4 mg/day divided; comes in 0.25, 0.5 & 1 mg tabs.

midazolam (Versed®) DRUG INFO

3 to 4 times as potent as diazepam (Valium®). Dissolves in aqueous solution, thus less burning and phlebitis than diazepam. At physiologic pH, is lipid soluble and readily crosses BBB. Greater amnestic effect than diazepam. Excellent anticonvulsant properties. Given IM, onset occurs at 15 min, peak at 30 min, duration 1-2 hrs[72].

Rx:

1. for **conscious sedation** (slow IVP): 1-2 mg over 2 min (do not exceed 2.5 mg with initial dose), wait 2-3 mins, and repeat up to total of 0.1-0.15 mg/kg. Reduce by at least 25% if opioids are also being used or in patients > 60 yrs. To maintain sedation, repeat doses of 25% of initial. Caution:

midazolam has been associated with respiratory arrest (even in young patients). Monitor patient continuously, use extra caution in elderly

2. for IM **pre-op**: 0.07-0.08 mg/kg (5 mg/70 kg) about 1 hr pre-op.
3. for induction for general anesthesia:
   A. initial dose (slow IVP) of:
      1. for unpremedicated average adult age ≤ 55 yrs: 0.25 mg/kg
      2. > 55 yrs, ASA class I or II: 0.2 mg/kg
      3. ASA III or IV: 0.15 mg/kg
   B. to maintain: repeat 25% of initial dose.

Midazolam drip:

Dilute 50 mg midazolam in 100 cc IV fluid (only glass bottle recommended, as plastic adsorbs midazolam); start at 1-2 mg/hr and titrate to desired level of sedation.

Table 3-13 Comparisons of oral benzodiazepines
(Taken from **The Medical Letter**, Vol. 30, pp. 28, 1988, with permission)

Generic name	Proprietary	Rapidity of onset	Duration	Typical daily dose
alprazolam	Xanax®	intermediate	intermediate	0.25-0.5 mg TID
chlordiazepoxide	Librium®	intermediate	long	5-10 mg TID-QID
clorazepate	Tranxene®	rapid	long	15-60 mg/d divided
diazepam	Valium®	rapid	long	2-10 mg BID-QID
lorazepam	Ativan®	intermediate	intermediate	1 mg BID-TID
flurazepam	Dalmane®	rapid to intermediate	long	30 mg
temazepam	Restoril®	intermediate to slow	intermediate	15-30 mg

BENZODIAZEPINE REVERSAL

flumazenil (Romazicon®) DRUG INFO

Competitively inhibits benzodiazepines **(BDZ)** at receptor sites. Since duration of action is shorter than most BDZs, resedation may occur, especially with large doses of BDZs given over a long procedure. BDZ antagonism begins < 2 mins after IV dose, peaks in 6-10 mins, and lasts ≈ 60 mins. Sedation is only partially reversed in some patients. Reversal of BDZ induced respiratory depression is partial or nil[73].

Contraindicated in patients chronically treated with BDZs (for seizures or for other indications) where antagonism may provoke a withdrawal syndrome and/or seizures. May provoke a panic attack. Not approved for use in pregnancy.

Rx To reverse BDZs used for conscious sedation or general anesthesia: 0.2 mg (2 ml) IV over 15 seconds; repeat at 1 minute intervals if level of reversal is inadequate up to a maximum of 1 mg (total of 5 doses). If resedation occurs, may repeat dosing at 20 minute intervals, keeping within a maximum of 3 mg per hour. For suspected overdosage, give 0.2 mg over 30 secs, wait 30 secs, then give 0.3 mg over 30 secs at 1 minute intervals up to 3 mg or until patient arouses.

3.3.4. Acid inhibitors

Stress ulcers in neurosurgery[7]

The risk of stress ulcers **(SU)** is high in critically ill patients with CNS pathology. 17% of SUs produce clinically significant hemorrhage. CNS risk factors include intracranial pathology: brain injury (especially Glasgow Coma scale score < 9), brain tumors, intracerebral hemorrhage, SIADH, CNS infection, ischemic CVA, as well as spinal cord injury. The odds are increased with the coexistence of extra-CNS risk factors including: long-term use of steroids (usually > 3 weeks), burns > 25% of body surface area, hypotension, respiratory failure, coagulopathies, renal or hepatic failure and sepsis.

CNS pathology, especially that involving the diencephalon or brain stem, can lead to reduction of vagal output which leads to hypersecretion of gastric acid and pepsin. There is a peak in acid and pepsin production 3-5 days after CNS injury.

Prophylaxis for stress ulcers

There is strong evidence that reduction of gastric acid (whether by antacids or agents that inhibit acid secretion) reduces the incidence of GI bleeding from stress ulcers in critically ill patients. Elevating gastric pH > 4.5 also inactivates pepsin.

Other therapies that don't involve alterations of pH that may be effective include sucralfate and enteral nutrition (controversial)[7]. Titrated antacids or sucralfate appear to be superior to H_2 antagonists in reducing the incidence of SUs.

Routine prophylaxis when steroids are used is not warranted unless one of the following risk factors are present: prior PUD, concurrent use of NSAIDs,

hepatic or renal failure, malnourishment, or prolonged steroid therapy > 3 weeks.

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NOTES

4. Neurology

4.1. Dementia

Definition: loss of intellectual abilities previously attained (memory, judgement, abstract thought, and other higher cortical functions) severe enough to interfere with social and/or occupational functioning[1]. Memory deficit is the cardinal feature, however, the DSM-IV definition requires impairment in at least one other domain (language, perception, visuospatial function, calculation, judgement, abstraction, problem-solving skills). Affects 3-11% of community-dwelling adults > 65 yrs of age, with a greater presence among institutionalized residents[2].

Risk factors: advanced age, family history of dementia, and apolipoprotein E-4 allele.

Delerium: AKA acute confusional state. Distinct from dementia, however, patients with dementia are at increased risk of developing delerium[3, 4]. A primary disorder of attention that subsequently affects all other aspects of cognition[5]. Often represents life-threatening illness, e.g. hypoxia, sepsis, uremic encephalopathy (also *see page 73*), electrolyte abnormality, drug intoxication, MI. 50% of patients die within 2 yrs of this diagnosis.

Unlike dementia, delerium has acute onset, motor signs (tremor, myoclonus, asterixis), slurred speech, altered consciousness (hyperalert/agitated or lethargic, or fluctuations), hallucinations may be florid. EEG → pronounced diffuse slowing.

Brain biopsy for dementia

Clinical criteria are usually sufficient for the diagnosis of most dementias. Biopsy should be reserved for cases of a chronic progressive cerebral disorder with an unusual clinical course where all other possible diagnostic methods have been exhausted and have failed to provide adequate diagnostic certainty[6]. Biopsy may disclose CJD, low grade astrocytoma, and AD among others. The high incidence of CJD among patients selected for biopsy under these criteria

necessitates appropriate precautions (see *Creutzfeldt-Jakob disease*, page 361). In a report of 50 brain biopsies performed to assess progressive neurodegenerative disease of unclear etiology[7], the diagnostic yield was only 20% (6% were only suggestive of a diagnosis, 66% were abnormal but nonspecific, 8% were normal). The yield was highest in those with focal MRI abnormalities. Among the 10 patients with diagnostic biopsies, the biopsy result led to a meaningful therapeutic intervention in only 4.

Recommendations

Based on the above, the following recommendations are made for patients with an otherwise unexplained neurodegenerative disease:

1. those with a focal abnormality on MRI: stereotactic biopsy
2. those without focal abnormality (possibly including SPECT or PET scan): brain biopsy should only be performed within an investigative protocol

Recommendations for specimen

Ideally the biopsy specimen should[8]:

1. be large enough (usually 1 cm^3)
2. be taken from an affected area
3. include grey and white matter
4. be handled carefully to minimize artifact (electrocautery should not be used on the specimen side of the incision)

4.2. Headache

Headache **(H/A)** may be broadly categorized as follows:

1. chronic recurring headaches
   A. vascular type (migraine): *see below*
   B. muscle contraction (tension) headaches
2. headache due to pathology
   A. systemic pathology
   B. intracranial pathology: a wide variety of etiologies including:
      1. subarachnoid hemorrhage: <u>sudden</u> onset, severe, usually with vomiting, apoplexy, focal deficits possible (*see* *page 1035* for

differential diagnosis of paroxysmal H/A)
2. increased intracranial pressure from any cause (tumor, communicating hydrocephalus, inflammation, pseudotumor cerebri…)
3. irritation or inflammation of meninges: meningitis
4. tumor: with or without elevated ICP (*see page 587*)

C. local pathology of the eye, nasopharynx, or extracranial tissues (including giant cell arteritis, *see page 74*)
D. following head trauma (postconcussive syndrome): *see page 910*
E. following craniotomy ("syndrome of the trephined"): *see page 149*

A severe new H/A, or a change in the pattern of a longstanding or recurrent H/A (including developing associated N/V, or an abnormal neurologic exam) warrants further investigation with CT or MRI[9].

Unilateral H/A that never changes side over a period ≥ 1 year warrants an MRI (this would be atypical in migraine and may be a presentation of an occipital AVM - *see page 1099*).

4.2.1. Migraine

Migraine attacks usually occur in individuals predisposed to the condition, and may be activated by factors such as bright light, stress, diet changes, trauma, administration of radiologic contrast media (especially angiography) and vasodilators.

CLASSIFICATION

See also index under *Headache*, e.g. for: crash migraine (thunderclap headache) *page 1035*, post-myelogram headache *page 58*…

COMMON MIGRAINE

Episodic H/A with N/V and photophobia, without aura or neurologic deficit.

CLASSIC MIGRAINE

Common migraine + aura. May have H/A with occasional focal neurologic deficit(s) that resolve completely in ≤ 24 hrs.

Over half of the transient neurologic disturbances are visual, and usually consist of positive phenomena (spark photopsia, stars, complex geometric

patterns, fortification spectra) which may leave negative phenomena (scotoma, hemianopsia, monocular or binocular visual loss…) in their wake. The second most common symptoms are somatosensory involving the hand and lower face. Less frequently, deficits may consist of aphasia, hemiparesis, or unilateral clumsiness. A slow march-like progression of deficit is characteristic. The risk of stroke is probably increased in patients with migraine[10].

COMPLICATED MIGRAINE

Occasional attacks of classic migraine with minimal or no associated H/A, and complete resolution of neurologic deficit in ≤ 30 days.

MIGRAINE EQUIVALENT

Neurologic symptoms (N/V, visual aura, etc.) without H/A (acephalgic migraine). Seen mostly in children. Usually develops into typical migraine with age. Aura may be shortened by opening and swallowing contents of a 10 mg nifedipine capsule[11].

HEMIPLEGIC MIGRAINE

H/A typically precedes hemiplegia which may persist even after H/A resolves.

CLUSTER HEADACHE

AKA histaminic migraine. Actually a neurovascular event, distinct from true migraine. Recurrent unilateral attacks of severe pain. Usually oculofrontal or oculotemporal with occasional radiation into the jaw, usually recurring on the same side of the head. Ipsilateral autonomic symptoms (conjunctival injection, nasal congestion, rhinorrhea, lacrimation, facial flushing) are common. Partial Horner's syndrome (ptosis and miosis) sometimes occurs. Male:female ratio is ≈ 5:1. 25% of patients have a personal or family history of migraine.

Headaches characteristically have no prodrome, last 30-90 minutes, and recur one or more times daily usually for 4-12 weeks, often at a similar time of day, following which there is typically a remission for an average of 12 months[12].

Treatment for cluster H/A (prophylaxis is only minimally effective):

Treatment is difficult because there is no prodrome and the H/A often stop after 1-2 hrs. Treatment of acute attacks includes:

- 100% O_2 by face mask with patient sitting for ≤ 15 min or until attack

aborted

- ergotamine
- SQ sumatriptan: usually aborts attack within 15 minutes
- steroids
- refractory cases may be considered for:
    - percutaneous radiofrequency sphenopalatine ganglion blockade[13]
    - occipital nerve stimulation[14]
    - hypothalamic deep brain stimulation

BASILAR ARTERY MIGRAINE

Essentially restricted to adolescence. Recurrent episodes lasting minutes to hours of transient neurologic deficits in distribution of vertebrobasilar system. Deficits include: vertigo (most common), gait ataxia, visual disturbance (scotomata, bilateral blindness), dysarthria, followed by severe H/A and occasionally nausea and vomiting[15]. Family history of migraine is present in 86%.

4.2.2. Post LP (myelogram) H/A

AKA "postspinal headache" or "spinal headache". May also follow procedures other than LP/myelogram, such as dural opening (*see page 450*). Can also occur with spontaneous intracranial hypotension (*see page 305*).

Clinical features

Important distinctive characteristic: H/A occurs when patient is erect, and is completely or partially (but significantly) relieved when recumbent. May be associated with nausea, vomiting, dizziness, or visual disturbances.

Time course: Most post-LP headaches **(PLPHA)** have a delayed onset 24-48 hrs after the LP, and although they may occur weeks post-LP, most also develop within 3 days. The duration of PLPHA varies, with a mean of 4 days[16], and reports of duration of months[17] and even > 1 year[18].

Pathophysiology

Thought to be due to continued CSF leakage through the hole in the dura[19], which reduces the CSF "cushion" of the brain. In the upright position, the pull of

gravity on the brain produces traction on the blood vessels and any structures tethering the brain to the painsensitive dura. CSF may sometimes be demonstrable in the epidural space.

Epidemiology following LP

Reported incidence range is 2-40% (typically ≈ 20%), higher after diagnostic LP than for epidural anesthesia[16].

For variables in LP that impact upon the risk of PLPHA, *see page 204*

TREATMENT FOR H/A FOLLOWING LP

Initial "conservative" measures include:

1. flat in bed for at least 24 hrs
2. hydration (PO or IV)
3. analgesics for H/A
4. tight abdominal binder
5. desoxycortisone acetate 5 mg IM q 8 hrs[16]
6. caffeine sodium benzoate 500 mg in 2 cc IV q 8 hrs up to 3 d max (70% of patients had relief with 1 or 2 injections)[20]
7. high-dose steroids: report of success in a case of intracranial hypotension associated with spontaneous slit ventricles tapering down from a starting dose of dexamethasone 20 mg/day[21]
8. blood patch if refractory (*see below*)

EPIDURAL BLOOD PATCH

For refractory post-lumbar puncture or post-myelogram H/A. Works in one application in over 90% of cases, may be repeated if ineffective[17]. Theoretical risks: infection, cauda equina compression, failure to relieve H/A.

Technique

Accessing epidural space (one of several techniques): proceed as routine LP. When ligaments are traversed, and needle tip is nearing spinal canal, stylet is removed. Then, either place drop of sterile saline in hub (hanging drop technique) and advance while watching for it to be drawn into needle as epidural space is entered, or gently try injecting air with small syringe (preferably glass) while advancing, when the epidural space is entered, resistance to injection disappears, but CSF cannot be aspirated.

A venipuncture site is prepared aseptically. 10 ml of the patient's blood is with-drawn. After verifying CSF cannot be aspirated through the spinal needle, the blood is injected into the epidural space. After 30 minutes supine, patient may ambulate ad lib.

4.3. Parkinsonism

Parkinsonism may be primary or secondary to other conditions. All result from a relative loss of dopamine mediated inhibition of the effects of acetylcholine in the basal ganglia.

IDIOPATHIC PARALYSIS AGITANS (IPA)

Classical Parkinson's disease AKA shaking palsy.

Clinical

Affects ≈ 1% of Americans > age 50 yrs[22]. Male:female ratio is 3:2. Not clearly environmentally or genetically induced, but may be influenced by these factors.

The classic triad is shown in *Table 4-1*. Other signs may include: postural instability, micrographia, mask-like facies. Gait consists of small, shuffling steps (marche á petits pas) or festinating gait.

Table 4-1 Classic triad of Parkinson's disease

- tremor (resting, 4-7/second)
- rigidity (cogwheel)
- bradykinesia

Clinically distinguishing IPA from secondary parkinsonism (*see below*): May be difficult early. IPA generally exhibits gradual onset of bradykinesia with tremor that is often asymmetrical, and initially responds well to levodopa. Other disorders are suggested with rapid progression of symptoms, when the initial response to levodopa is equivocal, or when there is early midline symptoms (ataxia or impairment of gait and balance, sphincter disturbance…) or the presence of other features such as early dementia, sensory findings, profound orthostatic hypotension, or abnormalities of extraocular movements[23, 24].

Pathophysiology

Degeneration primarily of pigmented (neuromelaninladen) dopaminergic neurons of the pars compacta of the substantia nigra, resulting in reduced levels of dopamine in the neostriatum (caudate nucleus, putamen, globus pallidus). This decreases the activity of inhibitory neurons with predominantly D2 class of dopamine receptors which project directly to the internal segment of the globus pallidus **(GPi)**, and also increases (by loss of inhibition) activity of neurons with predominantly D1 receptors which project indirectly to the globus pallidus externa **(GPe)** and subthalamic nucleus[25]. The net result is increased activity in GPi which has inhibitory projections to the thalamus which then suppresses activity in the supplemental motor cortex among other locations.

Histologically: **Lewy bodies** (eosinophilic intraneuronal hyaline inclusions) are the hallmark of IPA.

SECONDARY PARKINSONISM

The differential diagnosis includes the following etiologies of secondary parkinsonism or Parkinson-like conditions (some referred to as "Parkinson plus"):

1. **olivopontocerebellar degeneration (OPC)**
2. striato-nigral degeneration **(SND)**: more aggressive than parkinsonism
3. postencephalitic parkinsonism: followed an epidemic of encephalitis lethargica (von Economo disease) in the 1920's, victims are no longer living. Distinguishing features: oculogyric crisis, tremor involves not only extremities but also trunk and head, asymmetrical, no Lewy bodies
4. progressive supranuclear palsy **(PSNP)**: impaired vertical gaze (*see below*)
5. multiple system atrophy (Shy-Drager syndrome): *see below*
6. drug induced: includes:
   A. prescription drugs (elderly females seem more susceptible)
      1. antipsychotics (AKA neuroleptics): haloperidol (Haldol®) which works by blocking postsynaptic dopamine receptors
      2. phenothiazine antiemetics: prochlorperazine (Compazine®)
      3. metoclopramide (Reglan®)
      4. reserpine

   B. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine): a commercially available chemical intermediate which is also a by-product of the synthesis of MPPP (a meperidine analog) that was synthesized and self-injected by a graduate student[26], and later

produced by illicit drug manufacturers to be sold as “synthetic heroin” and unwittingly injected by some IV drug abusers in northern California in 198327. MPTP was subsequently discovered to be a potent neurotoxin for dopaminergic neurons. As a rule, the response to levodopa is dramatic, but short-lived

C. there is an as yet unproven assertion that methylenedioxymethamphetamine **(MDMA)** AKA “ecstasy” (on the street), may hasten the onset of Parkinsonism

7. toxic: poisoning with
   A. carbon monoxide: symmetric low densities in the globus pallidus on CT
   B. manganese: may be seen in miners, welders, and pyrotechnics workers. Manganese is excreted by the liver, ∴ people with hepatic insufficiency are more susceptible. Imaging: symmetrical high signal abnormalities on T1WI primarily in the globus pallidus with essentially no findings on T2WI or GRASS (almost pathognomonic)
8. ischemic (lacunes in basal ganglia): produces so-called **arteriosclerotic parkinsonism** AKA vascular parkinsonism: “lower-half” parkinsonism (gait disturbance predominates[28]). Also causes pseudobulbar deficits, emotional lability. Tremor is rare
9. posttraumatic: parkinsonian symptoms may occur in chronic traumatic encephalopathy (dementia pugilistica, *see page 911*). There are usually other features not normally present in IPA (e.g. cerebellar findings)
10. normal pressure hydrocephalus **(NPH)**: urinary incontinence… (*see page 329*)
11. neoplasm in the region of the substantia nigra
12. Riley-Day (familial dysautonomia)
13. parkinson-dementia complex of Guam: classic IPA + amyotrophic lateral sclerosis **(ALS)**. Pathologically has features of parkinsonism and Alzheimer’s disease but no Lewy bodies nor senile plaques
14. Huntington’s disease **(HD)**: whereas adults typically show chorea, when HD manifests in a young person it may resemble IPA
15. (spontaneous) intracranial hypotension may present with findings mimicking IPA (*see page 305*)

Multiple system atrophy ***(MSA)***

AKA Shy-Drager syndrome. Parkinsonism (indistinguishable from IPA),

PLUS idiopathic orthostatic hypotension, *PLUS* other signs of autonomic nervous system **(ANS)** dysfunction (ANS findings may precede parkinsonism and may include urinary sphincter disturbance and hypersensitivity to noradrenaline or tyramine infusions). Degeneration of preganglionic lateral horn neurons of thoracic spinal cord. Unlike IPA, most do not respond to dopa therapy. NB: classic IPA may eventually produce orthostatic hypotension from inactivity or as a result of progressive autonomic failure.

Progressive supranuclear palsy (PSNP)

AKA Steele-Richardson-Olszewski syndrome[29].

Triad:

1. progressive supranuclear ophthalmoplegia (chiefly vertical gaze): paresis of voluntary vertical eye movement, but still moves to vertical doll's eyes maneuver
2. pseudobulbar palsy (mask-like facies with marked dysarthria and dysphagia, hyperactive jaw jerk, emotional incontinence usually mild)
3. axial dystonia (especially of neck and upper trunk)

Associated findings: subcortical dementia (inconstant), motor findings of pyramidal, extrapyramidal and cerebellar systems. Average age of onset: 60 yrs. Males comprise 60%. Response to anti-parkinson drugs is usually very short lived. Average survival after diagnosis: 5.7 yrs.

Differentiating from Parkinson's disease (IPA):

Patients with PSNP have a pseudo-parkinsonism. They have mask facies, but do not walk bent forward (they walk erect), and they do not have a tremor. They tend to fall backwards.

Course

1. early:
   A. many falls: due to dysequilibrium + downgaze palsy (can't see floor)
   B. eye findings may be normal initially, subsequently may develop difficulty looking down (especially to command, less to following), calorics have normal tonic component but absent nystagmus (cortical component)
   C. slurred speech
   D. personality changes

    E. difficulty eating: due to pseudobulbar palsy + inability to look down at food on plate
2. late:
    A. eyes fixed centrally (no response to oculocephalics or oculovestibulars): ocular immotility is due to frontal lobe lesions
    B. neck stiffens in extension (retrocollis)

SURGICAL TREATMENT FOR PARKINSON'S DISEASE

Before the introduction of L-dopa in the late 1960's, stereotactic thalamotomy was widely used for Parkinson's disease. The location ultimately targeted for lesioning was the ventrolateral nucleus. The procedure worked better for relieving the tremor than for the bradykinesia, however it was the latter symptom that was most disabling. This procedure cannot be done bilaterally without significant risk to speech function. The procedure fell out of favor when more effective drugs became available[30].

See *Surgical treatment of Parkinson's disease* on page 532 for further information.

4.4. Multiple sclerosis

Key concepts:

- an idiopathic demyelinating disease of thc CNS producing exacerbating and remitting symptoms disseminated in space and time
- classic clinical findings: optic neuritis, paresthesias, INO and bladder symptoms
- diagnostic criteria (McDonald criteria) use clinical and/or lab results (MRI, CSF…) to stratify patients as: MS, probable MS, or not MS
- MRI: multiple usually enhancing lesions involving optic nerves & white matter of brain (especially periventricular white matter), cerebellum and spinal cord

An idiopathic demyelinating disease (affecting only white matter) of the cerebrum, optic nerves, and spinal cord (especially corticospinal tracts and the posterior columns). Does not affect *peripheral* myelin. Produces multiple plaques of various age in diffuse locations in the CNS, especially in the

periventricular white matter. Lesions initially evoke an inflammatory response with monocytes and lymphocytic perivascular cuffing, but with age settle down to glial scars.

EPIDEMIOLOGY

Usual age of onset: 10-59 years, with the greatest peak between ages 20-40 years. Female to male ratio: 2:1.

Prevalence varies with latitude, and is < 1 per 100,000 near the equator, and is ≈ 30-80 per 100,000 in the northern U.S. and Canada.

CLINICAL

Causes exacerbations and remissions in various locations in the CNS (dissemination in space and time). Common symptoms: visual disturbances (diplopia, blurring, field cuts or scotoma), spastic paraparesis, and bladder disturbances. Nomenclature for the time course of MS is shown in *Table 4-2*[31]. Relapsing-remitting MS is the most common pattern (≥ 70%) at onset, and has the best response to therapy, but > 50% of cases eventually become secondary progressive MS. Only 10% have primary progressive MS, and these patients tend to be older at onset (40-60 years) and frequently develop progressive myelopathy[32]. Progressive relapsing MS is very uncommon.

Deficits present > 6 months usually persist.

Table 4-2 Clinical categories of MS

Category	Definition
relapsingremitting	episodes of acute worsening with recovery and a stable course between relapses
secondary progressive	gradual neurologic deterioration ± superimposed acute relapses in a patient who previously had relapsing-remitting MS
primary progressive	gradual, nearly continuous neurologic deterioration from the onset of symptoms
progressive relapsing	gradual neurologic deterioration from the onset of symptoms, but with subsequent superimposed relapses

Differential diagnosis

The plethora of possible signs and symptoms in MS causes the differential diagnosis to extend to almost all conditions causing focal or diffuse dysfunction of the CNS. Conditions that may closely mimic MS clinically and on diagnostic testing include:

1. acute disseminated encephalomyelitis **(ADEM)**: generally monophasic. May also have CSF-OCB. Corpus callosum involvement is uncommon
2. CNS lymphoma: *see page 673*
3. other closely related demyelinating diseases: e.g. Devic syndrome (*see page 1187*)
4. vasculitis
5. encephalitis: patients are usually very ill
6. chronic white matter changes: seen in older patients

Signs and symptoms

Visual disturbances: Disturbances of visual acuity may be caused by optic or retrobulbar neuritis which is the presenting symptom of MS in 15% of cases, and which occurs at some time in 50% of MS patients. The percentage of patients with an attack of optic neuritis and no prior attack that will go on to develop MS ranges from 17-87% depending on the series[33]. Symptoms: acute visual loss in one or both eyes with mild pain (often on eye movement).

Diplopia may be due to internuclear ophthalmoplegia **(INO)** (*see page 834*) from a plaque in the MLF. INO is an important sign because it rarely occurs in other conditions besides MS or brainstem stroke.

Motor findings: Extremity weakness (mono, para, or quadriparesis) and gait ataxia are among the most common symptoms of MS. Spasticity of the LEs is often due to pyramidal tract involvement. Scanning speech results from cerebellar lesions.

Sensory findings: Posterior column involvement often causes loss of proprioception. Paresthesias of extremities, trunk, or face occur. Lhermitte's sign (electric shock-like pain radiating down the spine on neck flexion) is common, but is not pathognomonic. Trigeminal neuralgia occurs in ≈ 2%, and is more often bilateral and occurs at a younger age than the population in general[34].

Mental disturbances: Euphoria (la belle indifference) and depression occur in ≈ 50% of patients.

Reflex changes: Hyperreflexia and Babinski signs are common. <u>Abdominal cutaneous reflexes</u> disappear in 70-80%.

GU symptoms: Urinary frequency, urgency, and incontinence are common. Impotence in males and reduced libido in either sex is often seen.

DIAGNOSTIC CRITERIA

No single clinical feature or diagnostic test is adequate for the accurate diagnosis of MS. Therefore, clinical information is integrated with paraclinical studies. Diagnosing MS after a single, acute remitting clinically isolated syndrome **(CIS)** is very risky. 50-70% of patients with a CIS suggestive of MS will have multifocal MRI abnormalities characteristic of MS. The presence of these MRI abnormalities increases the risk of developing MS in 1-3 years (with greater prognostic significance than CSF-OCB). The more MRI lesions, the higher the risk[35]. Criteria for the diagnosis of MS[36] follows.

DEFINITIONS[36, 37]

1. attack (exacerbation, relapse): neurologic disturbance lasting > 24 hrs[38] typical of MS when clinicopathological studies determine that the cause is demyelinating or inflammatory lesions
2. remission: ≥ 30 days should separate the onset of the first attack from the onset of a second
3. historical information: reporting of symptoms by the patient (confirmation by observer desirable), adequate to locate a lesion of MS, and has no other explanation (i.e. manifestations must not be attributable to another condition)
4. clinical evidence (signs): neuro dysfunction recorded by competent examiner
5. paraclinical evidence: tests or procedures demonstrating CNS lesion which has not produced signs; e.g. Uhthoff phenomenon or sign (worsening of symptoms with hot bath or shower), BAER, imaging procedures (CT, MRI), expert urological assessment
6. typical of MS: signs & symptoms **(S/S)** known to occur frequently in MS. Thus excludes gray matter lesions, peripheral nervous system lesions, and non-specific complaints such as H/A, depression, convulsive seizures, etc.
7. separate lesions: S/S cannot be explained on basis of single lesion (optic neuritis of both eyes simultaneously or within 15 days represents single lesion)
8. laboratory support: in this study, the only considerations were CSF oligoclonal bands **(CSF-OCB)** (*see below*) (OCB must not be present in serum) or increased CSF IgG production **(CSF-IgG)** (serum IgG must be normal). This assumes that syphilis, SSPE, sarcoidosis, etc. have been ruled out

Table 4-3 Diagnostic criteria for MS[36]

Clinical presentation	Additional data needed to diagnose MS
≥ 2 attacks; objective clinical evidence of ≥ 2 lesions	none*
≥ 2 attacks; objective clinical evidence of 1 lesion	demonstrate dissemination in *space* by: • MRI† or • ≥ 2 MS-compatible lesions on MRI PLUS positive CSF‡ or • await additional clinical attack implicating another site
1 attack; objective clinical evidence of ≥ 2 lesions	demonstrate dissemination in *time* by • MRI§ or • second clinical attack
1 attack; objective clinical evidence of 1 lesion (mono-symptomatic presentation; clinically isolated syndrome)	demonstrate dissemination in *space* by: • MRI† or • ≥ 2 MS-compatible lesions on MRI PLUS positive CSF‡ or and demonstrate dissemination in *time* by: • MRI§ or • second clinical attack
insidious neurological progression suggestive of MS	positive MCSF‡ and demonstrate dissemination in *space* by A. ≥ 9 T2WI lesions on MRI or B. ≥ 2 lesions in spinal cord or C. 4-8 brain + 1 spinal cord lesion or D. abnormal VEPΔ + (4-8 brain lesions or< 4 brain lesions + 1 spinal cord lesion on MRI) and demonstrate dissemination in *time* by A. MRI§ or B. continued progression for 1 year

* additional tests not required. If MRI or CSF test s are done and are negative, apply extreme caution in diagnosing MS

† must meet criteria in *Table 4-4*

‡ positive CSF showing oligoclonal bands, see *Table 4-6*

§ dissemination in *time* on MRI must meet the criteria in *Table 4-5*

Δ abnormal visual evoked potential as seen in MS (delay with well-preserved wave-form)

Diagnosis of MS

The “McDonald criteria” are shown in *Table 4-3*[36]. Preferred terms:

- MS
- possible MS (at risk for MS but diagnosis is equivocal)

• not MS

MRI

MRI is the preferred imaging study in evaluating MS[39] and can demonstrate dissemination of lesions in time and space. Recommended[36] brain MRI criteria for diagnosing MS are shown in *Table 4-4*[40, 41]. Lesions are normally > 3 mm diameter[36]. MRI shows multiple white matter abnormalities in 80% of patients with MS (compared to 29% for CT)[42, 43]. Lesions are high signal on T2WI, and acute lesions tend to enhance with gadolinium more than old lesions do. Periventricular lesions may blend in with the signal from CSF in the ventricles on T2WI, these lesions are shown to better advantage on proton density images as higher intensity than CSF. These lesions are ovoid and are oriented perpendicular to the ependymal surface and are sometimes called **Dawson's fingers**.

Spinal cord lesions normally show little or no swelling, should be ≥ 3 mm but < 2 vertebral segments, occupy only a portion of the cross-section of the cord, and must be hyperintense on T2WI[44].

Specificity of MRI is ≈ 94%[45], however, encephalitis as well as UBOs seen in aging may mimic MS lesions. DWI should be normal, however plaques can sometimes exhibit "shine through" (*see page 132*) so the ADC map must be checked to rule-out infarct.

Table 4-4 Brain MRI criteria for MS

3 of the following 4 criteria*
1. 1 gadolinium-enhancing lesion or, if no gadolinium enhancing lesions, then 9 T2WI lesions
2. ≥ 1 infratentorial lesion
3. ≥ 1 juxtacortical lesion (i.e. involving subcortical u fibers)
4. ≥ 3 periventricular lesions

* 1 spinal cord lesion can be substituted for 1 brain lesion

Focal **tumefactive demyelinating lesions (TDL)** may occur in isolation or, more commonly, in patients with established MS (concentric sclerosis of Balo). TDL may represent an intermediate position between MS and ADEM[46]. TDLs tend to be symmetric. TDLs may enhance, and show perilesional edema (but less than MS) and thus be mistaken for neoplasms. Biopsy results may be confusing. MRS may not be able to differentiate from neoplasm[47].

Table 4-5 MRI criteria for dissemination of lesions in time

1. if first MRI occurs ≥ 3 months after the onset of the clinical event, then a gadolinium enhancing lesion in a different location than

	that implicated by the event meets the criteria. If there is no enhancing lesion, a follow-up MRI is required*. A new enhancing or T2WI lesion meets the criteria
	2. if first MRI is < 3 months from onset, a second MRI ≥ 3 months from onset showing a new gadolinium enhancing lesion meets the criteria. If no enhancing lesion, a 3rd MRI ≥ 3 months from the first showing a new enhancing or T2WI lesion meets the criteria

* timing not critical, but 3 months is recommended[48]

CSF

CSF analysis can support the diagnosis in some cases, but cannot document dissemination of lesions in time or space. The CSF in MS is clear and colorless. The OP is normal. Total CSF protein is < 55 mg/dl in ≈ 75% of patients, and < 108 mg/dl in 99.7% (values near 100 should prompt a search for an alternative diagnosis). The WBC count is ≤ 5 cells/μl in 70% of patients, and only 1% have a count > 20 cells/μl (high values may be seen in the acute myelitis).

In ≈ 90% of patients with MS, CSF-IgG is increased relative to other CSF proteins, and a characteristic pattern occurs. Agarose gel electrophoresis shows a few IgG bands in the gamma region (**oligoclonal bands**) that are not present in the serum. CSF-OCB are not specific for MS, and can occur in CNS infections and less commonly with strokes or tumors. The predictive value of the absence of IgG in a patient with suspected MS has not been satisfactorily elucidated.

Recommended criteria have been published[49], most of which pertain to specifics of laboratory analysis, pertinent clinical excerpts are shown in *Table 4-6*.

Table 4-6 CSF criteria for MS

1. qualitative assessment of IgG is the most informative analysis
2. analysis should be performed on unconcentrated CSF and must be compared to simultaneously run serum sample in the same assay
3. quantitative analysis should be made in terms of one of the 5 recognized staining patterns for OCB
4. all other tests performed on the CSF (including WBC, protein & glucose, lactate) should be taken into consideration
5. if clinical suspicion is high but CSF results are equivocal, negative or show only a single band, consider repeating the LP
6. quantitative IgG is a complementary test, but is not a substitute for qualitative IgG testing

4.5. Motor neuron diseases

Degenerative diseases of motor neurons. For comparison of upper motor neuron **(UMN)** with lower motor neuron **(LMN)** and the paralysis they produce, *see page 786*.

Three patterns of involvement:

1. mixed UMN & LMN degeneration: amyotrophic lateral sclerosis **(ALS)** (*see below*). The most common of the motor neuron diseases
2. UMN degeneration: **primary lateral sclerosis**. Rare, onset after age 50. No LMN signs. Slower progression than ALS (yrs to decades). Pseudobulbar palsy is common[50]. Usually does not shorten longevity. May present with falling due to balance problems or low back and neck pain due to axial muscle weakness
3. LMN degeneration: progressive muscular atrophy **(PMA)** and spinal muscular atrophy **(SMA)**

4.5.1. Amyotrophic lateral sclerosis

Key concepts:

- degeneration of anterior horn cells and corticospinal tracts in the cervical spine and medulla (bulb) of unknown etiology
- a mixed upper and lower motor neuron disease (UMN → mild spasticity in LEs; LMN → atrophy and fasciculations in UEs)
- clinically: progressive muscle wasting, weakness, and fasciculations
- no cognitive, sensory, nor autonomic dysfunction

In the U.S. amyotrophic lateral sclerosis **(ALS)** is AKA Lou Gehrig's disease. Some-times AKA motor neuron *disease* (singular).

Epidemiology[33]

Prevalence: 4-6/100,000. Incidence: 0.8-1.2/100,000.

Familial in 8-10% of cases. Familial cases usually follow autosomal dominant inheritance, but occasionally demonstrate a recessive pattern.

Onset usually after 40 years of age.

Pathology

Etiology is not known with certainty. Histology: degeneration of anterior horn alpha-motoneurons (in the spinal cord and in brain stem motor nuclei) (LMNs) and corticospinal tracts (UMNs). Produces mixed UMN & LMN findings, with a great deal of variability depending on which predominates at any given time.

Clinical

Characterized by progressive muscle wasting, weakness, and fasciculations.

Involvement is of voluntary muscles, sparing the voluntary eye muscles and urinary sphincter.

Classically, presents initially with weakness and atrophy of the hands (lower motor neuron) with spasticity and hyperreflexia of the lower extremities (upper motor neuron). However, LEs may be hyporeflexic if the lower motor neuron deficits predominate.

Dysarthria and dysphagia are caused by a combination of upper and lower motor neuron pathology. Tongue atrophy and fasciculations may also occur.

Although cognitive deficits are generally considered to be absent in ALS, in actuality 1-2% of cases are associated with dementia, and cognitive changes may occasionally predate the usual features of ALS[51].

Differential diagnosis

At times, it may be very difficult to distinguish ALS from cervical spondylotic myelopathy. See *page 489* for a discussion of differentiating features.

Diagnostic studies

EMG: Not absolutely necessary to make diagnosis in most cases. Fibrillations and positive sharp waves are found in advanced cases (may be absent early, especially if upper motor neuron pathology predominates). LMN findings in the LE in the absence of lumbar spine disease, or fibrillation potentials in the tongue are suggestive of ALS.

LP (CSF): May have slightly elevated protein.

Treatment

Ongoing trials with riluzole (Rilutek®), which inhibits the presynaptic release of glutamate, indicate that doses of 50-200 mg/d increases tracheostomy-free survival at 9 & 12 months, but the improvement is more modest or may be non-existent by ≈ 18 months[52-54]. At the time of this writing, the drug is available only for premarketing trials, and cannot be procured commercially.

Much of care is directed towards minimizing disability:

1. aspiration may be treated with
    - A. tracheostomy
    - B. gastrostomy tube to allow continued feeding

C. vocal cord injection with Teflon

2. spasticity that occurs when upper motor neuron deficits predominate may be treated (usually with short-lived response) with:

   A. baclofen: also may relieve the commonly occurring cramps (*see page 537*)

   B. diazepam

Prognosis

Most patients die within 5 years of onset (median survival: 3-4 yrs). Those with prominent oropharyngeal symptoms may have a shorter life-span usually due to complications of aspiration.

4.6. Guillain-Barré syndrome

Key concepts:

> • acute onset of peripheral neuropathy with progressive muscle weakness (more severe proximally) with areflexia, reaches maximum over 3 days to 3 weeks
> • cranial neuropathy: also common, may include facial diplegia, ophthalmoplegia
> • little or no sensory involvement (paresthesias are not uncommon)
> • onset often 3 days-5 weeks following viral URI, immunization, *Campylobacter jejuni* enteritis, or surgery
> • pathology: focal segmental demyelination with endoneurial monocytic infiltrate
> • elevated CSF protein without pleocytosis (albuminocytologic dissociation)

Guillain-Barré syndrome **(GBS)** AKA acute polyradiculoneuritis, among others, is actually a collection of syndromes having inflammatory polyradiculoneuropathy in common. Its most frequent form is acute inflammatory demyelinating polyradiculoneuropathy **(AIDP)**. First described as an ascending paralysis, most forms are characterized by symmetric weakness and areflexia. Mild cases may present only with ataxia, whereas fulminant cases may ascend to complete tetraplegia with paralysis of respiratory muscles and cranial nerves. There are also a number of variants (*see page 67*).

GBS is the most common acquired demyelinating neuropathy. Incidence is ≈ 1-3/100,000. The lifetime risk for any one individual getting GBS is ≈ 1/1,000.

GBS is triggered by both humoral and cell mediated autoimmune response to an immune sensitizing event. Frequent (but not essential) antecedents: viral infection, surgery, immunization, mycoplasma infection, enteral infection with *Campylobacter jejuni* (≈ 4 days of intense diarrhea). Higher frequency in the following conditions than in general population: Hodgkin's disease, lymphoma, lupus.

Most cases involve antibodies to gangliosides and glycolipids in peripheral myelin (axon antibodies occur in some forms). For unknown reasons serum creatine kinase can be mildly elevated, and may correlate with muscle type pain[55].

Diagnostic criteria[56]

1. features required for diagnosis:
   A. progressive motor weakness of more than 1 limb (from minimal weakness ± ataxia to paralysis, may include bulbar or facial or EOM palsy). Unlike most neuropathies, proximal muscles are affected more than distal
   B. areflexia (usually universal, but distal areflexia with definite hyporeflexia of biceps and knee jerks suffices if other features consistent)
2. features strongly supportive of diagnosis:
   A. clinical features (in order of importance)
      1. progression: motor weakness peaks at 2 wks in 50%, by 3 wks in 80%, and by 4 wks in > 90%
      2. relative symmetry
      3. mild sensory symptoms/signs (e.g. mild paresthesias in hands or feet)
      4. cranial nerve involvement: facial weakness in 50%, usually bilateral. GBS presents initially in EOMs or other Cr. N. in < 5% of cases. Oropharyngeal muscles may be affected
      5. recovery usually by 2-4 wks after progression stops, may be delayed by months (most patients recover functionally)
      6. autonomic dysfunction (may fluctuate): tachycardia and other arrhythmias, postural hypotension, HTN, vasomotor symptoms
      7. afebrile at onset of neuritic symptoms
      8. variants (not ranked):

a. fever at onset of neuritic symptoms
b. severe sensory loss with pain
c. progression > 4 wks
d. cessation of progression without recovery
e. sphincter dysfunction (usually spared): e.g. bladder paralysis
f. CNS involvement (controversial): e.g. ataxia, dysarthria, Babinski signs

B. CSF: **albuminocytologic dissociation** (↑ protein without pleocytosis)
1. protein: elevated after 1 wk of symptoms, > 55 mg/dl
2. cells: 10 or fewer mononuclear leukocytes/ml
3. variants
a. no CSF protein rise 1-10 wks after onset (rare)
b. 11-50 monocytes/ml
c. electrodiagnostics: 80% have NCV slowing or block at some time (may take several weeks in some). NCV usually < 60% of normal, but not in all nerves

3. features casting doubt on diagnosis:
A. marked, persistent, asymmetry of weakness
B. persistent bowel or bladder dysfunction
C. > 50 monocytes/ml CSF
D. PMNs in CSF
E. sharp sensory level

4. features of conditions in the differential diagnosis (*see below*)

GUILLAIN-BARRÉ VARIANTS

A number of variants have been described (some may simply be incomplete forms of typical Guillain-Barré). Autonomic dysfunction may occur in some.

Miller-Fisher variant of GBS: Ataxia, areflexia and ophthalmoplegia. May also have ptosis. 5% of cases of GBS. Serum marker: anti-GQ1b antibodies.

Acute motor axonal neuropathy (AMAN): This variant and AIDP are the most common to follow *Campylobacter jejuni* enteritis.

Pharyngeal-cervical-brachial variant: Facial, oropharyngeal, cervical, and UE weakness, sparing the LEs.

Pure sensory variant: Sensory loss accompanied by areflexia.

Atypical GBS: May be accompanied by rhabdomyolysis[57].

DIFFERENTIAL DIAGNOSIS

Also see conditions in the differential diagnosis under *Myelopathy* on page 1185

1. Guillain-Barré syndrome (including one of its variants)
2. critical illness polyneuropathy: EMG: ↓ CMAP & SNAP (*see page 794*)
3. current hexacarbon abuse: volatile solvents (n-hexane, methyl n-butyl ketone), glue sniffing
4. **acute intermittent porphyria (AIP)**: a disorder of porphyrin metabolism. CSF protein is not elevated in AIP. Recurrent painful abdominal crises are common. Check urine delta-aminolevulinic acid or porphobilinogen
5. recent diphtheritic infection: diphtheritic polyneuropathy has a longer latency and a slower crescendo of symptoms
6. lead neuropathy: UE weakness with wrist drop. May be asymmetrical
7. poliomyelitis: usually asymmetric, has meningeal irritation
8. hypophosphatemia (may occur in chronic IV hyperalimentation)
9. botulism: difficult to distinguish clinically from GBS. Normal NCV and a facilitating response to repetitive nerve stimulation on electrodiagnostics
10. toxic neuropathy (e.g. from nitrofurantoin, dapsone, thallium or arsenic)
11. tick paralysis: may cause an ascending motor neuropathy without sensory impairment. Careful examination of the scalp for tick(s)
12. **chronic immune demyelinating polyradiculoneuropathy (CIDP)** AKA chronic relapsing GBS, chronic relapsing polyneuritis[58]. Similar to GBS, but long time course (symptoms must be present > 2 mos). CIDP produces progressive, symmetrical, proximal & distal weakness, depression of muscle stretch reflexes, and variable sensory loss. Cranial nerves are usually spared (facial muscles may be involved). Balance difficulties are common. Need for respiratory support is rare. Peak incidence: age 40-60 yrs. Electrodiagnostics and nerve biopsy findings are indicative of demyelination. CSF findings are similar to GBS (*see above*). Most respond to immunosuppressive therapy (especially prednisolone & plasmapheresis) but relapses are common. Refractory cases may be treated with IV gamma-globulin, cyclosporin-A[59], total body lymphoid irradiation or interferon-α[60]
13. critical illness *myopathy*: Muscles not excitable with direct stimulation. EMG: low or normal CMAP with normal SNAP. Muscle biopsy: abnormalities may range from Type II fiber atrophy to necrosis (severe necrosis may not recover)
14. motor neuron disease: AKA ALS. Hyperreflexia in LEs (*see page 65*)

15. myasthenia gravis: weakness worsens towards the end of the day and with repeat efforts. Positive assay for circulating anti-acetylcholine receptor antibodies
16. spinal cord injury

IMAGING

No characteristic finding, however, diffuse enhancement of cauda equina and nerve roots occurs in up to 95% of cases[61] (for Differential diagnosis, see *page 1230*). Thought to be due to disruption of the blood-nerve barrier from inflammation. Conspicuous nerve root enhancement correlates with pain, GBS disability grade, and duration of recovery[61].

TREATMENT

Immunoglobulins may be helpful. In severe cases, early plasmapheresis hastens the recovery and reduces the residual deficit. Its role in mild cases is uncertain. Steroids are not helpful[62]. Mechanical ventilation and measures to prevent aspiration are used as appropriate. In cases of facial diplegia, the eyes must be protected from exposure (neuroparalytic) keratitis.

OUTCOME

Recovery may not be complete for several months. 35% of untreated patients have residual weakness and atrophy. Recurrence of GBS after achieving maximal recovery occurs in ≈ 2%.

4.7. Myelitis

AKA acute transverse myelitis **(ATM)**. The terminology is confusing: myelitis overlaps with “myelopathy”. Both are pathologic conditions of the spinal cord. Myelitis indicates inflammation, and etiologies include: infectious/post-infectious, autoimmune, and idiopathic. Myelopathy is generally reserved for compressive, toxic, or metabolic etiologies[63] (*see page 1185* for differential diagnosis).

ETIOLOGY

Many so-called “causes” remain unproven. Immunologic response against the CNS (most likely via cell mediated component) is the probable common

mechanism. Animal model: experimental allergic encephalomyelitis (requires myelin basic protein of CNS, not peripheral).

Generally accepted etiologies include:

1. infectious and post-infectious
   - A. primary infectious myelitis
     1. viral: poliomyelitis, myelitis with viral encephalomyelitis, herpes zoster, rabies
     2. bacterial: including tuberculoma of spinal cord
     3. spirochetal: AKA syphilitic myelitis. Causes syphilitic endarteritis
     4. fungal (aspergillosis, blastomycosis, cryptococcosis)
     5. parasitic (Echinococcus, cysticercosis, paragonimiasis, schistosomiasis)
   - B. post-infectious: including post-exanthematous, influenza
2. post-traumatic
3. physical agents
   - A. decompression sickness (dysbarism)
   - B. electrical injury*
   - C. post-irradiation
4. paraneoplastic syndrome (remote effect of cancer): most common primary is lung, but prostate, ovary and rectum have also been described[64]
5. metabolic
   - A. diabetes mellitus*
   - B. pernicious anemia*
   - C. chronic liver disease*
6. toxins
   - A. cresyl phosphates*
   - B. intraarterial contrast agents*
   - C. spinal anesthetics
   - D. myelographic contrast agents
   - E. following chemonucleolysis[65]
7. arachnoiditis
8. autoimmune
   - A. multiple sclerosis **(MS)**, especially Devic syndrome (*see page 1187*)
   - B. following vaccination (smallpox, rabies)
9. collagen vascular disease
   - A. systemic lupus erythematosus

B. mixed connective tissue disease

* items with an asterisk may be more properly associated with myelopathy rather than myelitis

CLINICAL

PRESENTATION

34 patients with ATM[66]: age of onset ranged 15-55 yrs (66% occurred in 3rd & 4th decade). 12 patients (35%) had a viral-like prodrome. Presenting symptoms are shown in *Table 4-7*. Other presenting symptoms of unspecified frequency[68]: fever and rash.

Table 4-7 Presenting symptoms in myelitis

Symptom	Series A*	Series B†
pain (back or radicular)	35%	35%
muscle weakness	32%	13%
sensory deficit or paresthesias	26%	46%
sphincter disturbance	12%	6%

* series A: 34 patients with ATM[66]

† series B: 52 patients with acute or subacute transverse myelitis[67]

Table 4-8 Level of sensory deficit

Level	%
cervical	8%
high thoracic	36%
low thoracic	32%
lumbar	8%
unknown	16%

Presenting level

The levels at presentation in 62 patients with ATM are shown in *Table 4-8*[68]. The thoracic level is the most common sensory level. ATM is rarely the presenting symptom of MS (≈ 3-6% of patients with ATM develop MS).

PROGRESSION

Progression is usually rapid, with 66% reaching maximal deficit by 24 hrs, however the interval between first symptom and maximal deficit varies from 2 hrs-14 days[68]. Findings at the time of maximal deficit are shown in *Table 4-9*.

EVALUATION

Myelogram, CT & MRI: no characteristic finding. One paper reports 2 patients with fusiform cord enlargement[69]. High resolution MRI with thin cuts may be able to demonstrate area of involvement within the cord. Patient should have imaging to R/O compressive lesion.

CSF: normal during acute phase in 38% of LPs. Remainder (62%) had elevated protein (usually > 40 mg%) or pleocytosis (lymphocytes, PMNs, or both) or both.

Table 4-9 Symptoms at time of maximal deficit (62 patients with ATM[68])

Symptom	%
sensory deficit or paresthesias	100%
muscle weakness	97%
sphincter disturbance (hesitancy, retention, overflow incontinence)	94%
pain in back, abdomen, or limbs	34%
fever	27%
nuchal rigidity	13%

EVALUATION SCHEME

In a patient developing acute myelopathy/paraplegia, especially when ATM is considered likely, the first test of choice is an emergency MRI. If not readily available, a myelogram (with CT to follow) directed at the region of the sensory level is performed (CSF may be sent in this circumstance once block is ruled out).

TREATMENT

Suggested efficacy of high-dose steroid treatment in 1 patient with ATM[70] (methylprednisolone 250 mg IV q 6 hrs **x** 24 hrs, 125 mg IV q 6 hrs **x** 24 hrs, 125 mg IV q 12 hrs **x** 48 hrs, then 30 mg PO q 6 hrs, tapered gradually. Regimen should probably be individualized based on response).

PROGNOSIS

In a series of 34 ATM patients with ≥ 5 yrs follow-up **(F/U)**[66]: 9 patients (26%) had good recovery (ambulate well, mild urinary symptoms, minimal sensory and UMN signs); 9 (26%) had fair recovery (functional gait with some degree of spasticity, urinary urgency, obvious sensory signs, paraparesis); 11 (32%) poor (paraplegic, absent sphincter control); 5 (15%) died within 4 mos of illness. 18 patients (62% of survivors) became ambulatory (in these cases, all could walk with support by 3-6 mos).

In a series of 59 patients[68] (F/U period unspecified): 22 (37%) had good recovery; 14 (24%) poor; 3 died in acute stage (respiratory insufficiency in 2, sepsis in 1). Recovery occurred between 4 weeks and 3 mos after onset (no improvement occurred after 3 mos).

4.8. Neurosarcoidosis

Key concepts:

- neurologic involvement of sarcoidosis (a systemic granulomatous disease)
- may produce multiple cranial nerve palsies
- the most common neurologic manifestation is diabetes insipidus
- corticosteroids are beneficial for systemic as well as neurologic involvement

Sarcoidosis is a granulomatous disease that is usually systemic, and may include the CNS (so-called **neurosarcoidosis** AKA neurosarcoid). Only 1-3% of cases have CNS findings without systemic manifestations[71]. The cause of the disease is unknown. An exaggerated cellular immune response for unknown reasons is the currently favored hypothesis. Organs commonly involved include lungs, skin, lymph nodes, bones, eyes, muscles, and parotid glands[33].

PATHOLOGY

CNS sarcoidosis primarily involves the leptomeninges, however parenchymal invasion often occurs. Adhesive arachnoiditis with nodule formation may also occur (nodules have a predilection for the posterior fossa). Diffuse meningitis or meningoencephalitis may occur, and may be most pronounced at the base of the brain (basal meningitis) and in the subependymal region of the third ventricle (including the hypothalamus).

Constant microscopic features of neurosarcoidosis include noncaseating

granulomas with lymphocytic infiltrates. Langhans giant cells may or may not be present.

EPIDEMIOLOGY

Incidence of sarcoidosis is ≈ 3-50 cases/100,000 population; neurosarcoidosis occurs in ≈ 5% of cases (reported range: 1-27%). In one series, the median age of onset of neurologic symptoms was 44 years.

CLINICAL FINDINGS

Clinical findings include multiple cranial nerve palsies in 50-70% (particularly facial n., including diplegia), peripheral neuropathy, and myopathy[72]. Occasionally the lesions may produce mass effect[73], and hydrocephalus may result from adhesive basal arachnoiditis. Patients may have low grade fever. Intracranial hypertension is common and may be dangerous. Hypothalamic involvement may produce disorders of ADH (diabetes insipidus, disordered thirst). Rare involvement of the pituitary may produce pituitary insufficiency. Seizures occur in 15%.

0.4% of patients with sarcoidosis develop spinal cord involvement[74], and in 16% of these, the spinal cord was the only identifiable site of involvement.

LABORATORY

CBC: mild leukocytosis and eosinophilia may occur.

Serum angiotensin-converting enzyme (ACE): abnormally elevated in 83% of patients with active pulmonary sarcoidosis, but in only 11% with inactive disease[75]. False positive rate: 2-3%; may also be elevated in primary biliary cirrhosis.

CSF: similar to any subacute meningitis: elevated pressure, mild pleocytosis (10-200 cells/mm^3) mostly lymphocytes, elevated protein (up to 2,000 mg/dl), mild hypoglycorrhachia (15-40 mg/dl), CSF ACE is elevated in ≈ 55% of cases with neurosarcoidosis (normal in patients with sarcoidosis not involving the CNS)[76]. No organisms are recovered on culture or gram stain.

IMAGING

CXR

Usually demonstrates characteristic findings of sarcoidosis (hilar adenopathy, mediastinal lymph nodes…).

MRI

Gadolinium enhancement of the leptomeninges and/or optic nerve may be the only abnormal finding(s). Lesions may be solitary or multiple, and may be located intra- or extraparenchymal, periventricular, and/or in basal cisterns. Lesions may be seen on FLAIR that would otherwise have been missed. Hydrocephalus may occur.

Gallium scan

Nuclear medicine scan with 67Ga citrate (*see page 141*). Described findings include:

1. Panda sign[77]: uptake in lacrimal glands, parotid glands & nasopharynx (normal). Not specific for sarcoidosis
2. lambda distribution[78]: uptake in hilar lymph nodes
3. leopard man sign[79]: diffuse dappled pattern due to uptake in soft tissues, skin, muscles, mediastinum, and lacrimal glands

Diagnosis

Differentiating granulomatous angiitis **(GA)** from neurosarcoidosis that involves only the CNS can be done on histologic criteria: the inflammatory reaction in sarcoidosis is not limited to the region immediately surrounding blood vessels as it is in GA, where extensive disruption of the vessel wall may occur.

Making the diagnosis is relatively easy when systemic involvement occurs: characteristic findings on CXR, biopsy of skin or liver nodules, muscle biopsy, serum ACE assay.

Isolated neurosarcoidosis may be more difficult to diagnose, and may require biopsy (*see below*).

Table 4-10 Differential diagnosis of neurosarcoidosis

1. Hodgkin's disease
2. chronic granulomatous meningitis:
A. Hansen's disease (leprosy)
B. syphilis
C. cryptococcosis
D. tuberculosis
3. multiple sclerosis
4. CNS lymphoma
5. pseudotumor cerebri
6. granulomatous angiitis

BIOPSY

In uncertain cases, biopsy may be indicated. Whenever possible, MRI should be used to localize a supratentorial region of involvement, and biopsy should include all layers of meninges and cerebral cortex. Cultures and stains for fungus and acid-fast bacteria (TB) should be performed in addition to microscopic examination.

TREATMENT

Antibiotics have not been proven to be of benefit. Immunosuppression primarily with corticosteroids are beneficial for systemic as well as neurologic involvement. Therapy may be initiated with prednisone 60 mg PO qd in adults, and tapered based on response. Therapy with cyclosporine may allow a reduction in steroid dosage in refractory cases[80]. Treatment for unresponsive cases include: methotrexate, cytoxan, cyclophosphamide, azathioprine, low dose XRT. CSF shunting is indicated if hydrocephalus develops.

PROGNOSIS

Usually a benign disease. Peripheral and cranial nerve palsies recover slowly.

4.9. Vascular dysautoregulatory encephalopathy

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES)

AKA reversible posterior leukoencephalopathy syndrome **(RPLS)**. A group of encephalopathies with characteristic pattern of widespread vasogenic brain edema seen on CT or MRI with some predominance in the parietal and occipital regions[81]. The most common PRES pattern involves watershed zones with involvement of the cortex, subcortical and deep white matter to a variable extent[81]. A small number of patients with PRES will go on to infarction.

Patients may present with headache, seizures, mental status changes and focal neurologic deficit. Intracerebral hemorrhage **(ICH)** and SAH may occur in up to 15%[81].

Associated findings and conditions: Includes:

1. **hypertensive encephalopathy**: commonly seen in the setting of subacute blood pressure elevations (as may occur with malignant hypertension).

Imaging studies show symmetric confluent lesions with mild mass effect and patchy enhancement primarily in the subcortical white matter of the occipital lobes[82] which may produce cortical blindness

A. moderate to severe hypertension is seen in ≈ 75% of patients with PRES[81] although the upper limits of autoregulation are often not reached

B. in addition to hemispheric patterns of edema isolated brain stem and cerebellar edema have been described. Posterior fossa edema has been reported to cause obstructive hydrocephalus in a severe case[83]

2. **preeclampsia/eclampsia** associated with cerebral edema[84]. The condition is often temporary, but (permanent) infarctions also occur. Restricted diffusion on MR imaging is seen in 11-26% of cases. Abnormal DWI areas on MRI may be associated with a worse prognosis[85]
   A. may present (e.g. with blindness) during pregnancy complicated by preeclampsia or eclampsia[86]
   B. may develop 4-9 days post-partum and may be associated with vasospasm[87]
   C. toxemia is attributed to the placenta. Delivery and removal of the placenta is felt to be curative[88]
3. **infection, sepsis and shock**: blood pressure was normal in 40% (edema was greater in the normotensive patients). Gram positive organisms predominate[89]
4. autoimmune disease: PRES has been described in patients with lupus, scleroderma, Wegener's granulomatosis and polyarteritis nodosa[81]. These patients often receive regimens of immunosuppressive medications (tacrolimus, cyclosporine), which have also been linked to cases of PRES
5. cancer chemotherapy: PRES occurs in patients receiving multi-drug high dose chemotherapy most commonly for hematopoietic malignancies
6. transplantation: PRES has been reported both with bone marrow and solid organ transplantation
   A. incidence: 3-16% with bone marrow transplantation depending on the preconditioning regimen and whether or not it is myeloablative[81]
   B. highest incidence in the first month following allogeneic bone marrow transplant[81]
   C. lower incidence following solid organ transplants. Occurs earlier following liver transplantation, usually within 2 months. Occurs later

in renal transplants[81]

7. cyclosporine post-transplant neurotoxicity[89]

Treatment

Disordered autoregulation mandates tight control of blood pressure to reduce the risk of ICH. The underlying cause needs to be addressed (i.e. control HTN, hold immunosuppressives or chemotherapeutics, delivery of the placenta, etc.).

UREMIC ENCEPHALOPATHIES

Imaging studies show multiple areas of symmetric edema in the basal ganglia, with severe cases developing focal infarcts with or without hemorrhage[82]. These disorders are associated with elevated BUN and include:

1. uremia
2. glomerulonephritis
3. hemolytic-uremic syndrome (HUS)
4. thrombotic thrombocytic purpura (TTP)

CROSSED CEREBELLAR DIASCHISIS

Hypometabolism of cerebellar cortex contralateral to a cerebral hemispheric lesion (lesions include: stroke, brain tumor…). Lesions in the motor cortex, anterior corona radiata, and thalamus produce the most marked suppression of metabolism. Theory: hypometabolism is due to disconnection of cerebro-ponto-cerebellar pathways → decreased oxygen and glucose consumption → decreased CO_2 production → local arterial constriction (down-regulation of cerebellar blood flow).

4.10. Vasculitis and vasculopathy

The vasculitides are a group of disorders characterized by inflammation and necrosis of blood vessels. Vasculitis may be primary or secondary. Those that may affect the CNS are listed in *Table 4-11*, all of these cause tissue ischemia (even after the inflammation is quiescent) that may range in effect from neuropraxia to infarction.

Table 4-11 Vasculitides that may affect the CNS[90]

Vasculitis	Frequency of neuro involvement	—TYPE OF CNS INVOLVEMENT*—				
		Acute encephalopathy	Seizure	Cranial nerve	Spinal cord	ICH or SAH
periarteritis nodosa† **(PAN)**‡	20-40%	++	++	+	+	+
hypersensitivity vasculitis†	10%	+	+	0	0	+
giant cell (temporal) arteritis†	10%	+	0	++	0	0
Takayasu's arteritis	10-36%	+	++	++	+	+
Wegener's granulomatosis†	23-50%	+	++	++	+	+
lymphomatoid granulomatosis†	20-30%	++	+	++	+	0
isolated angiitis of the CNS†	100%	++	+	++	++	+
Behçet's disease†	10-29%	++	+	++	+	+

* KEY: 0 = uncommon or unreported; + = not uncommon; ++ = common; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage

† see section that follows for these topics

‡ PAN: a group of disorders, frequencies may vary by subgroup

4.10.1. Giant cell arteritis (GCA)

Key concepts:

- formerly often referred to as temporal arteritis
- a chronic vasculitis of large and medium caliber vessels, primarily involving cranial branches of the arteries arising from the aortic arch
- age > 50 years; affects women twice as often as men
- important possible late complications: blindness, stroke, thoracic aortic aneurysms and aortic dissections
- temporal artery biopsy is recommended for all patients suspected of GCA
- corticosteroids are the drug of choice for treatment

AKA **temporal arteritis (TA)**, AKA cranial arteritis. A chronic granulomatous arteritis of unknown etiology involving primarily the cranial branches of the aortic arch (especially the external carotid artery **(ECA)**)[91], which if untreated, may lead to blindness. Takayasu's arteritis is similar to GCA, but tends to affect large arteries in young women; it has 2 phases: inflammatory (treated with corticosteroids) and stenotic (treated with arterial bypasses).

EPIDEMIOLOGY

Seen almost exclusively in Caucasians > 50 yrs age (mean age of onset is 70). Incidence: 17.8 per 100,000 people ≥ 50 years old[92] (range: 0.49-23). Prevalence: ≈ 223 (autopsy incidence may be much higher)[93]. More common in

northern latitudes and among individuals of Scandinavian descent[91]. Female:male ratio is ≈ 2:1 (reported range: 1.05-7.4:1). 50% of GCA patients also have polymyalgia rheumatica **(PMR)** (*see* *page 77*).

PATHOLOGY

Discontinuous (so-called “skip lesions”) inflammatory reaction of lymphocytes, plasma cells, macrophages, ± giant cells (if absent, intimal proliferation may be prominent); predominantly in media of involved arteries. Arteries preferentially involved include the ophthalmic and posterior ciliary branches and the entire distribution of the external carotid system (of which the STA is a terminal branch). Other arteries in the body may be involved (reported involvement of abdominal aorta, femoral, brachial and mesenteric arteries are rarely symptomatic). Unlike PAN, GCA generally spares the renal arteries.

CLINICAL

Various combinations of symptoms of giant cell arteritis are listed in *Table 4-12*. Onset is usually insidious, although occasionally it may be abrupt[95].

Table 4-12 Signs and symptoms of GCA[91, 94]

Frequent (> 50% of cases)	Occasional (10-50% of cases)	Rare (< 10% of cases)
H/A: 66% temporal artery tenderness	visual symptoms weight loss fever (low grade) proximal myalgias jaw claudication facial pain scalp tenderness	blindness extremity claudication tongue claudication ear pain synovitis stroke angina

Details of some findings:

1. H/A: the most common presenting symptom. May be nonspecific or located in one or both temporal areas, forehead, or occiput. May be superficial or burning with paroxysmal lancinating pain
2. symptoms relating to ECA blood supply (strongly suggestive of GCA, but not pathognomonic[96]): jaw claudication, tongue, or pharyngeal muscles
3. ophthalmologic symptoms: due to arteritis and occlusion of branches of ophthalmic artery or posterior ciliary arteries
   A. symptoms include: amaurosis fugax (precedes permanent visual loss in 44%), blindness, visual field cuts, diplopia, ptosis, ocular pain, corneal edema, chemosis
   B. blindness: incidence is ≈ 7%, and once it occurs, recovery of sight is unlikely

4. systemic symptoms
   A. nonspecific constitutional symptoms: fever (may present as FUO in 15% of cases), anorexia, weight loss, fatigue, malaise
   B. 30% have neurologic manifestations. 14% are neuropathies including mononeuropathies and peripheral polyneuropathies of the arms or legs[97]
   C. musculoskeletal symptoms
      1. PMR is the most common (occurs in 40% of patients): *see page 77*
      2. peripheral arthritis, swelling & pitting edema of hands & feet in 25%
      3. arm claudication from stenosis of subclavian and axillary arteries
   D. thoracic aortic aneurysms: 17 times as likely in GCA. Annual CXRs are adequate for screening
5. temporal arteries on physical examination may exhibit tenderness, swelling, erythema, reduced pulsations, or nodularity. Normal in 33%
6. the presence of systemic symptoms correlates with a lower incidence of blindness or stroke

Differential diagnosis:
1. periarteritis nodosa (PAN): *see page 77*
2. hypersensitivity vasculitis
3. atherosclerotic occlusive disease
4. malignancy: symptoms of low grade fever, malaise and weight loss
5. infection
6. trigeminal neuralgia: *see page 551*[7]. ophthalmoplegic migraine
8. dental problems

EVALUATION

Laboratory studies

1. ESR > 40 mm/hr (usually > 50) by Westergren method (if > 80 mm/hr with above clinical syndromes, highly suggestive of GCA). ESR is normal in up to 22.5%[98]
2. C-reactive protein: another acute phase reactant that is more sensitive than ESR. Has the advantage that it can be performed on frozen sera
3. CBC: may show mild normochromic anemia[99]

4. rheumatoid factor, ANA, and serum complement usually normal
5. LFTs abnormal in 30% (usually elevated alkaline phosphatase)
6. tests for rheumatoid factor and ANA are usually negative
7. temporal artery angiography not helpful (angiography elsewhere indicated if suspicion of large artery involvement exists)
8. CT: usually not helpful, one report described calcified areas corresponding to the temporal arteries[100]
9. temporal artery biopsy: *see below*

TEMPORAL ARTERY BIOPSY

Sensitivity and specificity are shown in *Table 4-13*.

Table 4-13 Temporal artery biopsy

sensitivity	≈ 90% (reported range[94, 101] is 9-97%)
specificity	near 100%
predictive value	≈ 94%

Indications and timing

Current recommendations: temporal artery biopsy in all patients suspected of having GCA[91].

Preferably, biopsy should be done before treatment is initiated[91]. However, pathologic changes be seen after more than 2 weeks of therapy[102], therefore do not withhold steroids to await biopsy.

Technique of temporal artery biopsy

Biopsy side of involvement if laterality exists. The yield is increased by removing a portion of artery that is involved clinically (a tender or inflamed segment)[103]. Mark the frontal branch of the STA with a skin marker (spare the main trunk and parietal branch if possible). Infiltrate local anesthetic. The incision is made parallel to the artery and if possible behind the hairline. The incision is taken down to the fascia of the temporalis muscle, to which the STA is superficial[104]. Optimal length of STA biopsy: 4-6 cm (if an abnormal segment of STA can be palpated, some say that a smaller biopsy to include this area may be sufficient, but this is probably unreliable as the muscle may be tender, etc.). Step-sectioning by pathologist through the entire length of the biopsy specimen

also increases the yield.

Frozen sections can be performed. Biopsy of the contralateral side if the first side is negative in cases where clinical suspicion is high increases the yield by 5-10%.

TREATMENT

No known cure. Steroids can produce symptomatic relief and usually prevent blindness (progression of ocular problems 24-48 hrs after institution of adequate steroids is rare). Totally blind patients or those with longstanding partial visual loss are unlikely to respond to any treatment.

1. for most cases:
   A. start with prednisone, 40-60 mg/d PO divided BID-QID (qod dosing is usually not effective in initial management) (*see* *page 31* for dosing forms…)
   B. if no response after 72 hrs, and diagnosis certain, ↑ to 10-25 mg QID
   C. once response occurs (usually within 3-7 days), give entire dose as q AM dose for 3-6 weeks until symptoms resolved and ESR normalizes (occurs in 87% of patients within ≈ 4 weeks) or stabilizes at < 40-50 mm/hr
   D. once quiescent, a gradual taper is performed to prevent exacerbations: reduce by 10 mg/d q 2-4 weeks to 40 mg/d, then by 5 mg/d q 2-4 wks to 20 mg/d, then by 2.5 mg/d q 2-4 wks to 5-7.5 mg/d which is maintained for several months, followed by 1 mg/d decrements q 1-3 mos (usual length of treatment is 6-24 mos; do not D/C steroids when ESR normalizes)
   E. if symptoms recur during treatment, prednisone dose is temporarily increased until symptoms resolve (isolated rise in ESR is not sufficient reason to increase steroids[91])
   F. patients should be followed closely for ≈ 2 years
2. in severely ill patients: methylprednisolone, 15-20 mg IV QID
3. anticoagulant therapy: controversial
4. acute blindness (onset within 24-36 hrs) in a patient with giant cell arteritis:
   A. consider up to 500 mg methylprednisolone IV over 30-60 mins (no controlled studies show reversal of blindness)
   B. some have used intermittent inhalation of 5% carbon dioxide and oxygen

OUTCOME

Complications of steroid therapy occur in ≈ 50% of patients (most are not life threatening, and include vertebral compression fractures in ≈ 36%, peptic ulcer disease in ≈ 12%, proximal myopathy, cataracts, exacerbation of diabetes; also see *Possible deleterious side effects of steroids*, page 33).

30-50% of patients will have spontaneous exacerbations of GCA (especially during the first 2 years) regardless of the corticosteroid regimen[91].

Survival parallels that of the general population. Onset of blindness after initiation of steroid therapy is rare.

4.10.2. Polymyalgia rheumatica (PMR)

PMR and giant cell arteritis **(GCA)** (*see page 74*) may be different points on a continuum of the same disease. Both have in increased frequency of HLA-DR[4] and systemic monocyte activation. 15% of patients with PMR eventually develop GCA.

Epidemiology[91]

Both GCA & PMR occur in people ≥ 50 years old. The incidence increases with age and peaks between 70-80 years and is higher at higher latitudes[91].

PMR is more common than GCA. Prevalence: 500/100,000)[105]. Incidence: 52.5 per 100,000 people ≥ age 50, higher in females (61.7) than males (39.9)[106].

Features[91]

- an inflammatory condition of unknown etiology
- clinical characteristics
    - A. aching and morning stiffness in the cervical region and shoulder & pelvic girdles lasting > 1 month. The pain usually increases with movement
        1. shoulder pain: present in 70-95% of patients. Radiates toward elbow
        2. hip & neck pain: 50-70%. Hip pain radiates towards knees
    - B. age ≥ 50 years
    - C. ESR ≥ 40 mm/hr (7-20% have normal ESR[107])
    - D. usually responds rapidly to low dose corticosteroids (≤ 20 mg

prednisone/day) *see below*

E. systemic symptoms (present in ≈ 33%): fever, malaise or fatigue, anorexia and weight loss

- favorable prognosis: usually remits in 1-3 years

Treatment

PMR responds to either to low doses of steroids[105] (10-20 mg prednisone/day) or sometimes to NSAIDs (response to steroids is much more rapid). The initial dose of steroids is maintained for 2-4 weeks, and then by ≤ 10% of the daily dose every 1-2 weeks[91] while observing for signs of GCA.

4.10.3. Other vasculitides

PERIARTERITIS NODOSA

AKA polyarteritis nodosa. Actually a group of necrotizing vasculitides, including:

- classic periarteritis nodosa **(PAN)**: a multisystem disease with inflammatory necrosis, thrombosis (occlusion), and hemorrhage of arteries and arterioles in every organ except lung & spleen. Nodules may be palpated along medium sized muscular arteries. Commonly produces mononeuritis multiplex, weight loss, fever, and tachycardia. Peripheral nerve manifestations are attributed to arteritic occlusion of vasa nervorum. CNS manifestations are uncommon and include H/A, seizures, SAH, retinal hemorrhages, and stroke in ≈ 13%
- allergic angiitis and granulomatosis (Churg-Strauss syndrome)
- systemic necrotizing vasculitis

These patients do better when treated with cyclophosphamide rather than steroids.

WEGENER'S GRANULOMATOSIS

A systemic necrotizing granulomatous vasculitis involving the respiratory tract (lung → cough/hemoptysis, and/or nasal airways → serosanguinous nasal drainage ± septal perforation → characteristic "saddle nose deformity") and frequently the kidneys (no reported cases of kidney involvement without respiratory)[108].

Nasal obstruction and crusting are the usual initial findings. Arthralgia (not true arthritis) is present in > 50%.

Neurologic involvement usually consists of cranial nerve dysfunction (usually II, III, IV, & VI; less often V, VII, & VIII; and least commonly IX, X, XI, & XII) and peripheral neuropathies, with diabetes insipidus (occasionally preceding other symptoms by up to 9 months). Focal lesions of the brain and spinal cord occur less frequently.

Differential diagnosis includes:

- "**lethal midline granuloma**" (may be similar or identical to polymorphic reticulosis) may evolve into lymphoma. May cause fulminant local destruction of the nasal tissue. Differentiation is crucial as this condition is treated by radiation; one should avoid immune suppression (e.g. cyclophosphamide). Probably does not involve true granulomas. Renal and tracheal involvement do not occur
- fungal disease: *Sporothrix schenckii* & Coccidioides may cause identical syndrome
- other vasculitides: especially Churg-Strauss syndrome (asthma and peripheral eosinophilia usually seen), and PAN (granulomas usually lacking)

LYMPHOMATOID GRANULOMATOSIS

Rare; affects mainly the lungs, skin (erythematous macules or indurated plaques in 40%) and nervous system (CNS in 20%, peripheral neuropathies in 15%). Sinuses, lymph nodes, and spleen are usually spared.

BEHÇET'S SYNDROME

Relapsing ocular lesions and recurrent oral and genital ulcers, with occasional skin lesions, thrombophlebitis, and arthritis 90. H/A occur in > 50%. Neurologic involvement includes pseudotumor, cerebellar ataxia, paraplegia, seizures, and dural sinus thrombosis. Only 5% have neurologic symptoms as the presenting complaint.

86% have CSF pleocytosis and protein elevation. Cerebral angiography is usually normal. CT may show focal areas of enhancing low density.

Steroids usually ameliorate ocular and cerebral symptoms, but usually have no effect on skin and genital lesions. Uncontrolled trials of cytotoxic agents → some benefit. Thalidomide may be effective (uncontrolled studies), but carries risk of serious adverse effects (teratogenicity, peripheral neuropathy…)[109].

Although painful, the disease is usually benign. Neurologic involvement portends a worse prognosis.

ISOLATED CNS VASCULITIS

AKA **isolated angiitis of the CNS**. Rare (≈ 20 cases reported[110] as of 1983); limited to vessels of CNS. Small vessel vasculitis is ≈ always present → segmental inflammation and necrosis of small leptomeningeal and parenchymal blood vessels with surrounding tissue ischemia or hemorrhage[90].

PRESENTATION

Combinations of H/A, confusion, dementia, and lethargy. Occasionally seizures. Focal and multifocal brain disturbance occurs in > 80%. Visual symptoms are frequent (secondary either to involvement of choroidal and retinal arteries, or to involvement of visual cortex → visual hallucinations).

EVALUATION

ESR & WBC count are usually normal. CSF may be normal or have pleocytosis and/or elevated protein. CT may show enhancing areas of low density.

Angiography (required for diagnosis): characteristically shows multiple areas of symmetrical narrowing ("string of pearls" configuration). If normal, it does not exclude diagnosis.

Histological diagnosis (recommended): all biopsy material should be cultured. Brain parenchyma biopsy infrequently shows vasculitis. Leptomeningeal biopsy invariably shows involvement.

HYPERSENSITIVITY VASCULITIS

Neurologic involvement is not a prominent feature of this group of vasculitides, which include:

- drug induced allergic vasculitis
- cutaneous vasculitis
- serum sickness: may → encephalopathy, seizures, coma, peripheral neuropathy and brachial plexopathy
- Henoch-Schönlein purpura

DRUG INDUCED VASCULITIS

A number of drugs are associated with the development of cerebral

vasculitis. These include methamphetamines (“speed”), cocaine (frank vasculitis occurs[111] but is rare), heroin and ephedrine.

4.10.4. Fibromuscular dysplasia

A vasculopathy (angiopathy) affecting primarily branches of the aorta, with renal artery involvement in 85% of cases (the most common site) and commonly associated with hypertension. The disease has an incidence of ≈ 1%, and results in multifocal arterial constrictions and intervening regions of aneurysmal dilatation.

The second most commonly involved site is the cervical internal carotid (primarily near C1-2), with fibromuscular dysplasia **(FMD)** appearing on 1% of carotid angiograms, making FMD the second most common cause of extracranial carotid stenosis[112]. Bilateral cervical ICA involvement occurs in ≈ 80% of cases. 50% of patients with carotid FMD have renal FMD. Patients with FMD have an increased risk of intracranial aneurysms and neoplasms, and are probably at higher risk of carotid dissection.

Table 4-14 Previous symptoms in 37 cases of aortocranial FMD[113]

Symptom	%
H/A	78%
mental distress	48%
tinnitus	38%
vertigo	34%
cardiac arrhythmia	31%
TIA	31%
syncope	31%
carotidynia	21%
epilepsy	15%
hearing impairment	12%
abdominal angina	8%
angina/MI	8%

Etiology

The actual etiology remains unknown, although congenital defects of the

media (muscular layer) and internal elastic layer of the arteries has been identified which may predispose the arteries to injury from otherwise well-tolerated trauma. A high familial rate of strokes, HTN, and migraine have supported the suggestion that FMD is an autosomal dominant trait with reduced penetrance in males[113].

Aneurysms and fibromuscular dysplasia

The reported incidence of aneurysms with FMD[114] ranges from 20-50%.

PRESENTATION

Most patients have recurrent, multiple symptoms shown in *Table 4-14*.

Up to 50% of patients present with episodes of transient cerebral ischemia or infarction. However, FMD may also be an incidental finding and some cases have been followed for 5 years without recurrence of ischemic symptoms suggesting that FMD may be a relatively benign condition.

Headaches are commonly unilateral and may be mistaken for typical migraine. Syncope may be caused by involvement of the carotid sinus.

Horner's syndrome occurs in ≈ 8% of cases. T-wave changes on EKG may be seen in up to one third of cases, and may be due to involvement of the coronary arteries.

Diagnosis

The "gold-standard" for the diagnosis of FMD is the angiogram. The three angiographic types of FMD[115] are shown in *Table 4-15*.

Treatment

Medical therapy including antiplatelet medication (e.g. aspirin) has been recommended.

Direct surgical treatment is problem ridden due to the difficult location (high carotid artery, near the base of the skull), and the friable nature of the vessels making anastomosis or arteriotomy closure difficult.

Transluminal angioplasty has achieved some degree of success. Carotid cavernous fistulas and arterial rupture have been reported as complications.

Table 4-15 Angiographic classification of FMD

Type	Findings
1	most common (80-100% of reported cases). Multiple, irregularly spaced, concentric narrowings with normal or dilated intervening segments giving rise to the so-called "**string of pearls**"

	appearance. Corresponds with arterial medial fibroplasia
2	focal tubular stenosis, seen in ≈ 7% of cases. Less characteristic for FMD than Type 1, and may also be seen in Takayasu's arteritis and other conditions
3	"atypical FMD". Rare. May take on various appearances, most commonly consisting of diverticular outpouchings of one wall of the artery

4.10.5. Miscellaneous vasculopathies

CADASIL

Key concepts:

- clinical: migraines, dementia, TIAs, psychiatric disturbances
- MRI: white matter abnormalities
- autosomal dominant inheritance
- anticoagulants controversial, generally discouraged

An acronym for Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy[116]. A familial disease with onset in early adulthood (mean age at onset: 45 ± 11 yrs), mapped to chromosome 19. Clinical and neuroradiologic features are similar to those seen with multiple subcortical infarcts from HTN, except there is no evidence of HTN. The vasculopathy is distinct from that seen in lipohyalinosis, arteriosclerosis and amyloid angiopathy, and causes thickening of the media of leptomeningeal and perforating arteries measuring 100-400 µm in diameter.

Clinical involvement: recurrent subcortical infarcts (84%), progressive or stepwise dementia (31%), migraine with aura (22%), and depression (20%). All symptomatic and 18% of asymptomatic patients had prominent subcortical white-matter and basal ganglia hyperintensities on T2WI MRI.

Treatment: Coumadin® is used by some.

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NOTES

5. Neuroanatomy and physiology

5.1. Surface anatomy

5.1.1. Cortical surface anatomy

Lateral cortical surface (*Figure 5-1*)

For abbreviations, *see Table 5-2* and *Table 5-1*. The MFG is usually more sinuous than the IFG or SFG, and it often connects to the pre-central gyrus via a thin isthmus[1]. The central sulcus joins the Sylvian fissure in only 2% of cases (i.e. in 98% of cases there is a "subcentral" gyrus). The intraparietal sulcus **(ips)** separates the superior and inferior parietal lobules. The IPL is composed primarily of the AG and SMG. The Sylvian fissure terminates in the SMG (Brodmann's area 40). The superior temporal sulcus terminates in the AG.

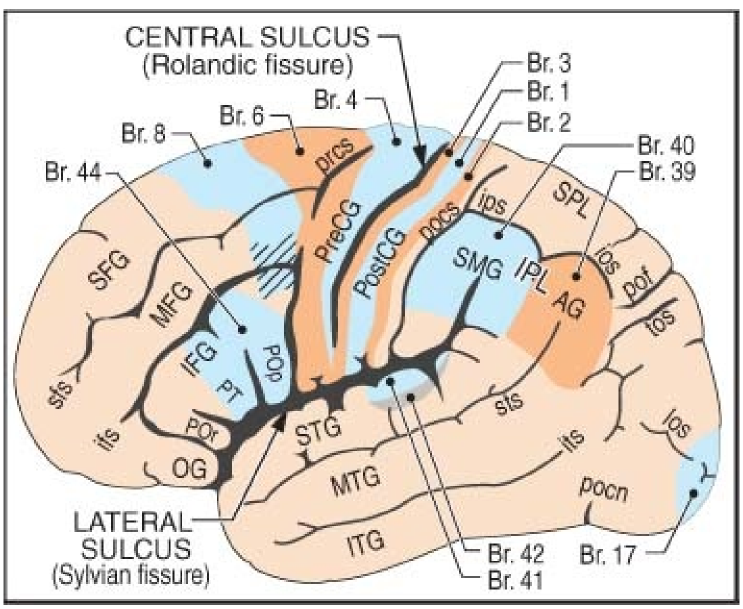

Figure 5-1 Left lateral cerebral cortical surface anatomy*

* Br. = Brodmann's area (shaded). See *Table 5-1* and *Table 5-2* for abbreviations (lowercase = sulci, UPPERCASE = gyri)

Brodmann’s areas

Figure 5-1 also identifies the clinically significant areas of Brodmann’s **(Br.)** map of the cytoarchitectonic fields of the human brain. Functional significance of these areas is as follows:

- Br. areas 3,1,2: primary somatosensory cortex
- Br. areas 41 & 42: primary auditory areas (transverse gyri of Heschl)
- Br. area 4: precentral gyrus, primary motor cortex (AKA “**motor strip**”). Large concentration of giant pyramidal cells of Betz
- Br. area 6: premotor area or supplemental motor area. Immediately anterior to motor strip, it plays a role in contralateral motor programming
- Br. area 44: (dominant hemisphere) **Broca’s area** (motor speech)[A]
- Br. area 17: primary visual cortex
- **Wernicke’s area** (language)[A]: in the dominant hemisphere, most of Br. area 40 and a portion of Br. area 39 (may also include ≈ posterior third of STG)
- the striped portion of Br. area 8 in *Figure 5-1* (frontal eye field) initiates voluntary eye movements to the opposite direction

A. language function cannot be reliably localized on anatomic grounds due to individual variability in its exact location; in order to perform maximal brain resections with minimal risk of aphasia, techniques such as intraoperative brain mapping[2] or looking for phase reversal on intraoperative cortical SSEP[3] should be employed (*see page 150*)

Medial surface

(*Figure 5-2*)

The cingulate sulcus terminates posteriorly in the **pars marginalis (pM)** (plural: partes marginales). On axial imaging, the pMs: are visible on 95% of CTs and 91% of MRIs[4], are usually the most prominent of the paired grooves straddling the midline, and they extend a greater distance into the hemispheres[4]. On axial CT, the pM is located slightly posterior to the widest biparietal diameter[4]; on the typically more horizontally oriented MRI slices the pM assumes a more posterior position. The pMs curve posteriorly in lower slices and anteriorly in higher slices (here, the paired pMs form the “**pars bracket**” - a characteristic “handlebar” configuration straddling the mid-line).

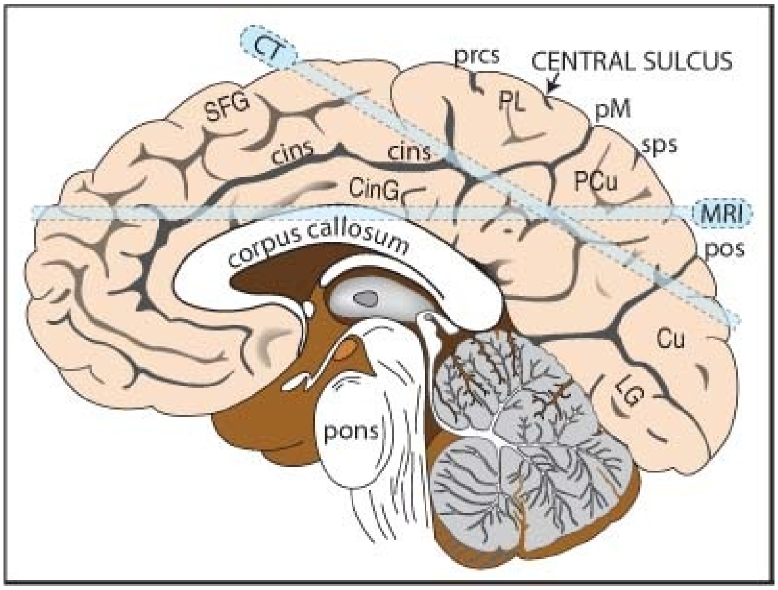

Figure 5-2 Medial aspect of the right hemisphere "CT" & "MRI" bars depict typical axial slice orientation for CT & MRI scans. See *Table 5-1* and *Table 5-2* for abbreviations

Central sulcus on axial imaging

See *Figure 5-3*. Identification is important to localize the motor strip (contained in the PreCG). The central sulcus **(CS)** is visible on 93% of CTs and 100% of MRIs[4]. It curves posteriorly as it approaches the interhemispheric fissure **(IHF)**, and often terminates in the paracentral lobule, just anterior to the pars marginalis **(pM)** within the pars bracket (*see above*)[4] (i.e. the CS often does not reach the midline).

Pointers:

- parieto-occipital sulcus **(pos)** (or fissure): more prominent over the medial surface, and on axial imaging is longer, more complex, and more posterior than the pars marginalis[5]
- post-central sulcus **(pocs)**: usually bifurcates and forms an arc or parenthesis ("lazy-Y") cupping the pM. The anterior limb does not enter the pM-bracket and the posterior limb curves behind the pM to enter the IHF

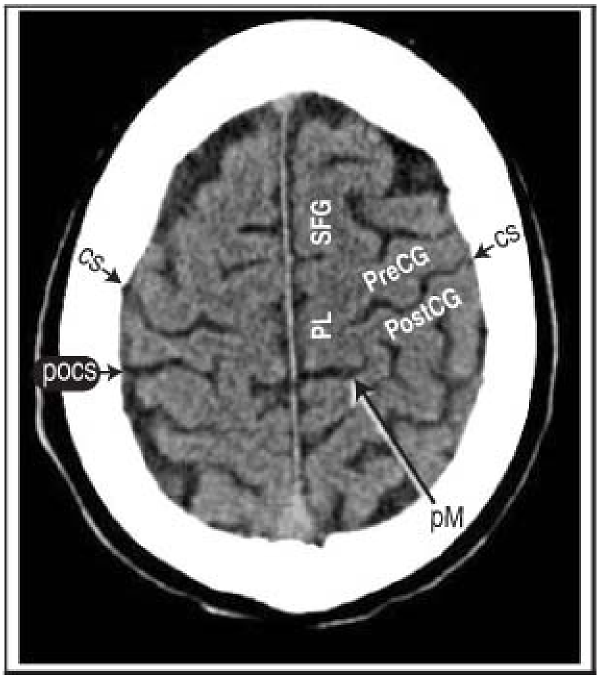

Figure 5-3 CT scan (upper cut) showing gyri/sulci. See *Table 5-1* and *Table 5-2* for abbreviations

Table 5-1 Cerebral sulci (abbreviations)

cins	cingulate sulcus
cs	central sulcus
ips-ios	intraparietal-intraoccipital sulcus
los	lateral occipital sulcus
pM	pars marginalis
pocn	pre-occipital notch
pocs	post-central sulcus
pof	parieto-occipital fissure
pos	parieto-occipital sulcus
prcs	pre-central sulcus
sfs, ifs	superior, inferior frontal sulcus
sps	superior parietal sulcus
sts, its	superior, inferior temporal sulcus
tos	trans occipital sulcus

Table 5-2 Cerebral gyri and lobules (abbreviations)

AG	angular gyrus
CinG	cingulate gyrus
Cu	cuneus
LG	lingual gyrus
MFG, SFG	middle & superior frontal gyrus
OG	orbital gyrus
PCu	precuneous
PreCG, PostCG	pre- and post-central gyrus
PL	paracentral lobule (upper SFG and PreCG and PostCG)
IFG POp PT POr	inferior frontal gyrus pars opercularis pars triangularis pars orbitalis
STG, MTG, ITG	superior, middle & inferior temporal gyrus
SPL, IPL	superior & inferior parietal lobule
SMG	supramarginal gyrus

5.1.2. Surface anatomy of the cranium

CRANIOMETRIC POINTS

See *Figure 5-4*.

Pterion: region where the following bones are approximated: frontal, parietal, temporal and sphenoid (greater wing). Estimated as 2 fingerbreadths above the zygomatic arch, and a thumb's breadth behind the frontal process of the zygomatic bone (blue circle in *Figure 5-4*).

Asterion: junction of lambdoid, occipitomastoid and parietomastoid sutures. Usually lies within a few millimeters of the posterior-inferior edge of the junction of the transverse and sigmoid sinuses (not always reliable[6] - may overlie either sinus).

Vertex: the top-most point of the skull.

Lambda: junction of the lambdoid and sagittal sutures.

Stephanion: junction of coronal suture and superior temporal line.

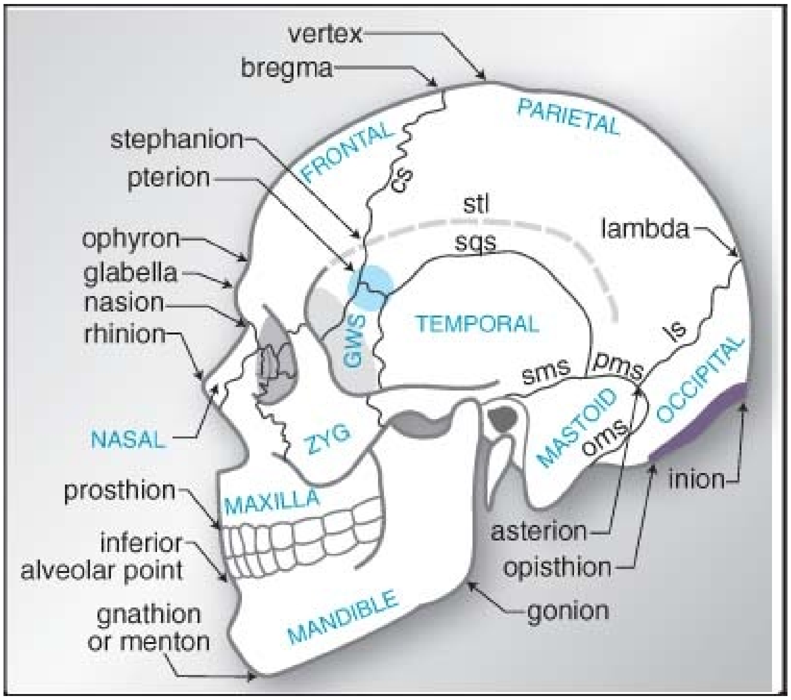

Figure 5-4 Craniometric points & cranial sutures.

Named bones appear in all upper case letters.
Abbreviations: GWS = greater wing of sphenoid bone, NAS = nasal bone, stl = superior temporal line, ZYG = zygomatic.
Sutures: cs = coronal, ls = lambdoid, oms = occipitomastoid, pms = parietomastoid, sms = squamomastoid, sqs = squamosal

Glabella: the most forward projecting point of the forehead at the level of the supraorbital ridge in the midline.

Opisthion: the posterior margin of the foramen magnum in the midline.

Bregma: the junction of the coronal and sagittal sutures.

Sagittal suture: midline suture from coronal suture to lambdoid suture. Although often assumed to overlie the superior sagittal sinus **(SSS)**, the SSS lies to the right of the sagittal suture in the majority of specimens[7] (but never by > 11 mm).

The most anterior mastoid point lies just in front of the sigmoid sinus[8].

RELATION OF SKULL MARKINGS TO CEREBRAL ANATOMY

Taylor-Haughton lines

Taylor-Haughton **(T-H)** lines can be constructed on an angiogram, CT scout film, or skull x-ray, and can then be re-constructed on the patient in the O.R.

based on visible external landmarks[9]. T-H lines are shown as dashed lines in *Figure 5-5*.

1. **Frankfurt plane**, AKA baseline: line from inferior margin of orbit through the upper margin of the external auditory meatus **(EAM)** (as distinguished from **Reid's base line**: from inferior orbital margin through the *center* of the EAM)[10 (p 313)]
2. the distance from the nasion to the inion is measured across the top of the calvaria and is divided into quarters (can be done simply with a piece of tape which is then folded in half twice)
3. posterior ear line: perpendicular to the baseline through the mastoid process
4. condylar line: perpendicular to the baseline through the mandibular condyle
5. T-H lines can then be used to approximate the sylvian fissure (*see below*) and the motor cortex (also *see below*)

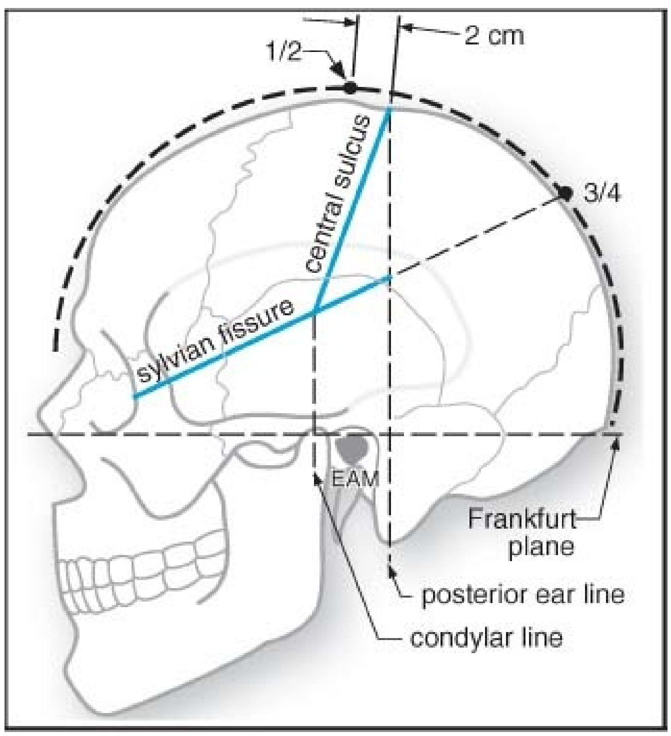

Figure 5-5 Taylor-Haughton lines and other localizing methods

Sylvian fissure AKA lateral fissure

Approximated by a line connecting the lateral canthus to the point 3/4 of the

way posterior along the arc running over convexity from nasion to inion (T-H lines).

Angular gyrus

Located just above the pinna, important on the dominant hemisphere as part of Wernicke's area. Note: there is significant individual variability in the location[2].

Angular artery

Located 6 cm above the EAM.

Motor cortex

Numerous methods utilize external landmarks to locate the motor strip (pre-central gyrus) or the central sulcus (Rolandic fissure) which separates motor strip anteriorly from primary sensory cortex posteriorly. These are just approximations since individual variability causes the motor strip to lie anywhere from 4 to 5.4 cm behind the coronal suture[11]. The central sulcus cannot even be reliably identified visually at surgery[12].

- method 1: the superior aspect of the motor cortex is almost straight up from the EAM near the midline
- method 2[13]: the central sulcus is approximated by connecting:
  - A. the point 2 cm posterior to the midposition of the arc extending from nasion to inion (illustrated in *Figure 5-5*), to
  - B. the point 5 cm straight up from the EAM
- method 3: using T-H lines, the central sulcus is approximated by connecting:
  - A. the point where the "posterior ear line" intersects the circumference of the skull (*see Figure 5-5*) (usually about 1 cm behind the vertex, and 3-4 cm behind the coronal suture), to
  - B. the point where the "condylar line" intersects the line representing the sylvian fissure
- method 4: a line drawn 45° to Reid's base line starting at the pterion points in the direction of the motor strip[14 (p 584-5)]

RELATIONSHIP OF VENTRICLES TO SKULL

Figure 5-6 shows the relationship of non-hydrocephalic ventricles to the skull in the lateral view. Some dimensions of interest are shown in *Table 5-3*[15].

In the non-hydrocephalic adult, the lateral ventricles lie 4-5 cm below the outer skull surface. The center of the body of the lateral ventricle sits in the midpupillary line, and the frontal horn is intersected by a line passing perpendicular to the calvaria along this line[16]. The anterior horns extend 1-2 cm anterior to the coronal suture.

Average length of third ventricle ≈ 2.8 cm.

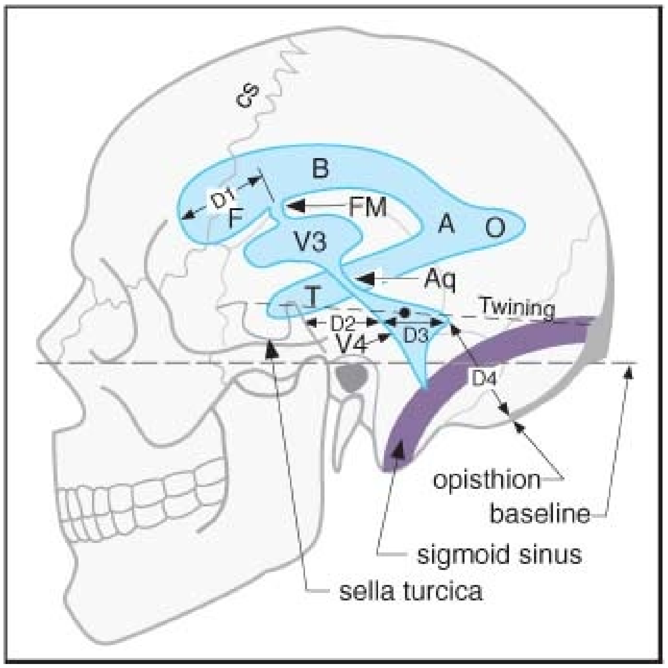

Figure 5-6 Relationship of ventricles to skull landmarks*

* Abbreviations: (F = frontal horn, B = body, A = atrium, O = occipital horn, T = temporal horn) of lateral ventricle. FM = foramen of Monro. Aq = sylvian aqueduct. V3 = third ventricle. V4 = fourth ventricle. cs = coronal suture. Dimensions D1-4 → *see Table 5-3*

Table 5-3 Dimensions from *Figure 5-6*

Dimension (*see Figure 5-6*)	Description	Lower limit (mm)	Average (mm)	Upper limit (mm)
D1	length of frontal horn anterior to FM		25	
D2	distance from clivus to floor of 4th ventricle at level of fastigium*	33.3	36.1	40.0
D3	length of 4th ventricle at level of fastigium*	10.0	14.6	19.0
D4	distance from fastigium* to opisthion	30.0	32.6	40.0

* the fastigium is the apex of the 4th ventricle within the cerebellum

5.1.3. Surface landmarks of spine levels

Estimates of cervical levels for anterior cervical spine surgery may be made using the landmarks shown in *Table 5-4*. Intraoperative C-spine x-rays are essential to verify these estimates.

The scapular spine is located at about T2-3.

The inferior scapular pole is ≈ T6 posteriorly.

Intercristal line: a line drawn between the highest point of the iliac crests across the back will cross the midline either at the interspace between the L4 and L5 spinous processes, or at the L4 spinous process itself.

Table 5-4 Cervical levels[17]

Level	Landmark
C1-2	angle of mandible
C3-4	1 cm above thyroid cartilage (≈ hyoid bone)
C4-5	level of thyroid cartilage
C5-6	crico-thyroid membrane
C6	carotid tubercle
C6-7	cricoid cartilage

5.2. Cranial foramina & their contents

Table 5-5 Cranial foramina and their contents*

Foramen	Contents
nasal slits	anterior ethmoidal nn., a. & v
superior orbital fissure	Cr. Nn. III, IV, VI, all 3 branches of V1 (ophthalmic division divides into nasociliary, frontal, and lacrimal nerves); superior ophthalmic vv.; recurrent meningeal br. from lacrimal a.; orbital branch of middle meningeal a.; sympathetic filaments from ICA plexus
inferior orbital fissure	Cr. N. V-2 (maxillary div.), zygomatic n.; filaments from pterygopalatine branch of maxillary n.; infraorbital a. & v.; v. between inferior ophthalmic v. & pterygoid venous plexus
foramen lacerum	usually nothing (ICA traverses the upper portion but doesn't enter, 30% have vidian a.)
carotid canal	internal carotid a., ascending sympathetic nerves
incisive	descending septal a.; nasopalatine nn.

foramen	
greater palatine foramen	greater palatine n., a., & v.
lesser palatine foramen	lesser palatine nn.
internal acoustic meatus	Cr. N. VII (facial); Cr. N. VIII (stato-acoustic) - (*see text* & *Figure 5-7* below)
hypoglossal canal	Cr. N. XII (hypoglossal); a meningeal branch of the ascending pharyngeal a.
foramen magnum	spinal cord (medulla oblongata); Cr. N. XI (spinal accessory nn.) entering the skull; vertebral aa.; anterior & posterior spinal arteries
foramen cecum	occasional small vein
cribriform plate	olfactory nn.
optic canal	Cr. N. II (optic); ophthalmic a.
foramen rotundum	Cr. N. V2 (maxillary div.), a. of foramen rotundum
foramen ovale	Cr. N. V3 (mandibular div.) + portio minor (motor for CrN V)
foramen spinosum	middle meningeal a. & v.
jugular foramen	internal jugular v. (beginning); Cr. Nn. IX, X, XI
stylomastoid foramen	Cr. N. VII (facial); stylomastoid a.
condyloid foramen	v. from transverse sinus
mastoid foramen	v. to mastoid sinus; branch of occipital a. to dura mater

* Abbreviations: a. = artery, aa. = arteries, v. = vein, vv. = veins, n. = nerve, nn. = nerves, br. = branch, Cr. N. = cranial nerve, fmn. = foramen, div. = division

Porus acusticus

AKA internal auditory canal (*see Figure 5-7*)

The filaments of the acoustic portion of VIII penetrate tiny openings of the lamina cribrosa of the cochlear area[18].

Transverse crest: separates superior vestibular area and facial canal (above) from the inferior vestibular area and cochlear area (below)[18].

Vertical crest (AKA Bill's bar): separates the meatus to facial canal anteriorly (containing VII and nervus intermedius) from the vestibular area posteriorly (containing the superior division of vestibular nerve).

The "5 nerves" of the IAC:

1. facial nerve (VII) (mnemonic: "7-up" as VII is in superior portion)
2. nervus intermedius: the somatic sensory branch of the facial nerve primarily innervating mechanoreceptors of the hair follicles on the inner surface of the pinna and deep mechanoreceptors of nasal and buccal cavities and chemoreceptors in the taste buds on the anterior 2/3 of the tongue
3. acoustic portion of the VIII nerve (mnemonic: "Coke down" for cochlear portion)
4. superior branch of vestibular nerve: passes through the superior vestibular area to terminate in the utricle and in the ampullæ of the superior and lateral semi-circular canals
5. inferior branch of vestibular nerve: passes through inferior vestibular area to terminate in the saccule

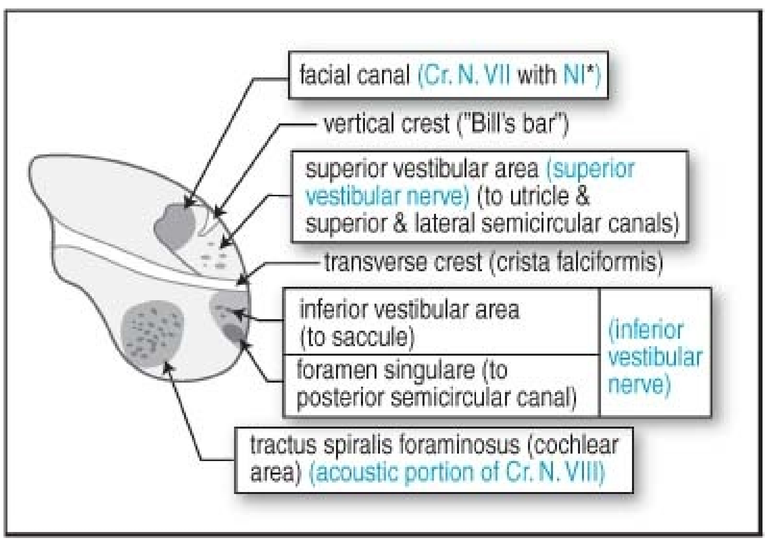

Figure 5-7 Right internal auditory canal (porus acusticus) & nerves

* NI = nervus intermedius

5.3. Cerebellopontine angle anatomy

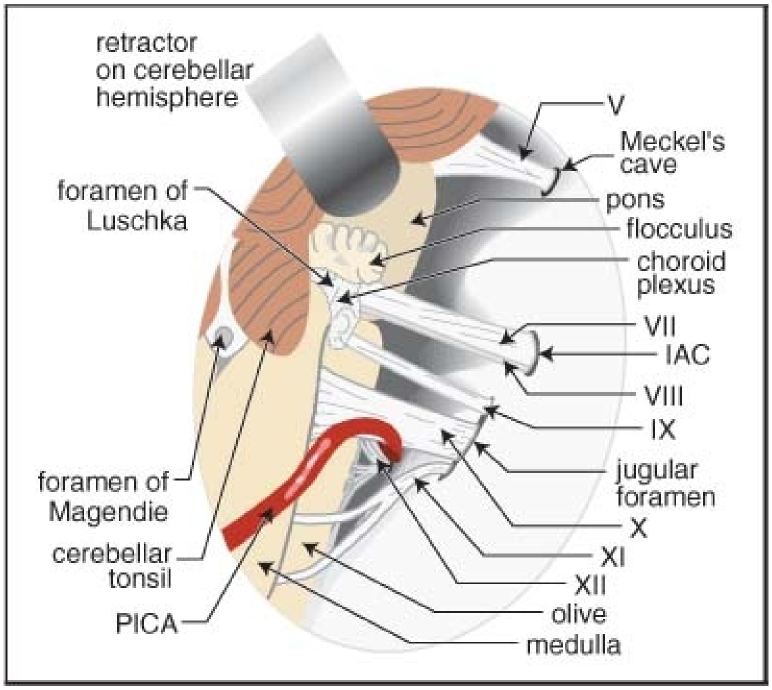

Figure 5-8 Normal anatomy of right cerebellopontine angle viewed from behind (as in a suboccipital approach)[18]

5.4. Occiptoatlantoaxial-complex anatomy

≈ 50% of head rotation occurs at the C1-2 (atlantoaxial) joint.

Ligaments of the occipito-atlanto-axial complex

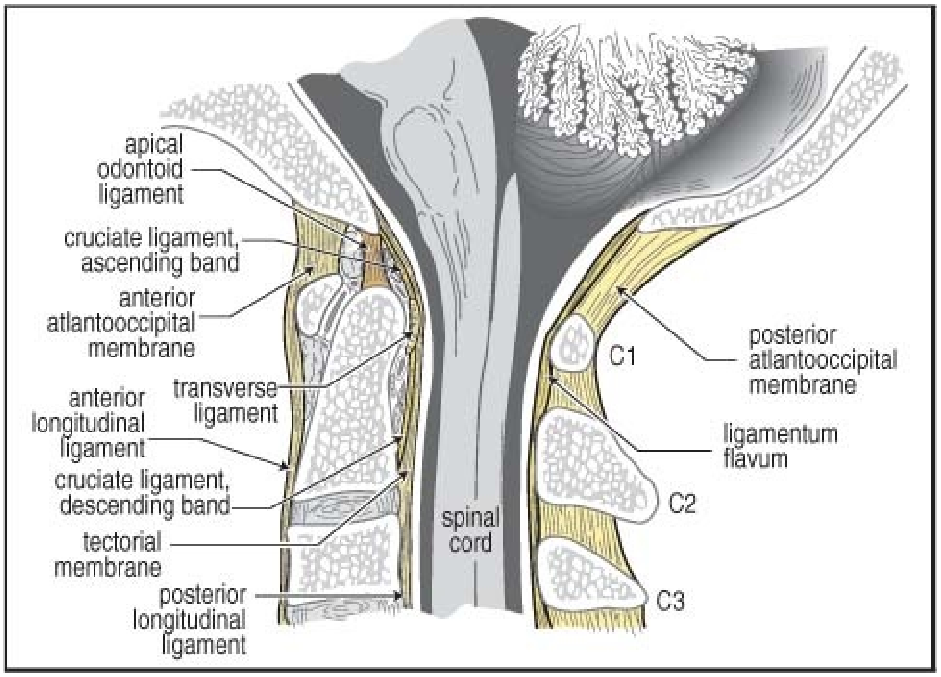

Figure 5-9 Sagittal view of the ligaments of the craniovertebral junction Modified with permission from "In Vitro Cervical Spine Biomechanical Testing" BNI Quarterly, Vol.9, No. 4, 1993

Stability of this joint complex is primarily due to ligaments, with little contribution from bony articulations and joint capsules (*see Figure 5-9* through *Figure 5-11*):

1. ligaments that connect the atlas to the occiput:
   A. anterior atlanto-occipital membrane: cephalad extension of the anterior longitudinal ligament. Extends from anterior margin of foramen magnum **(FM)** to anterior arch of C1
   B. posterior atlanto-occipital membrane: connects the posterior margin of the FM to posterior arch of C1
   C. the ascending band of the cruciate ligament

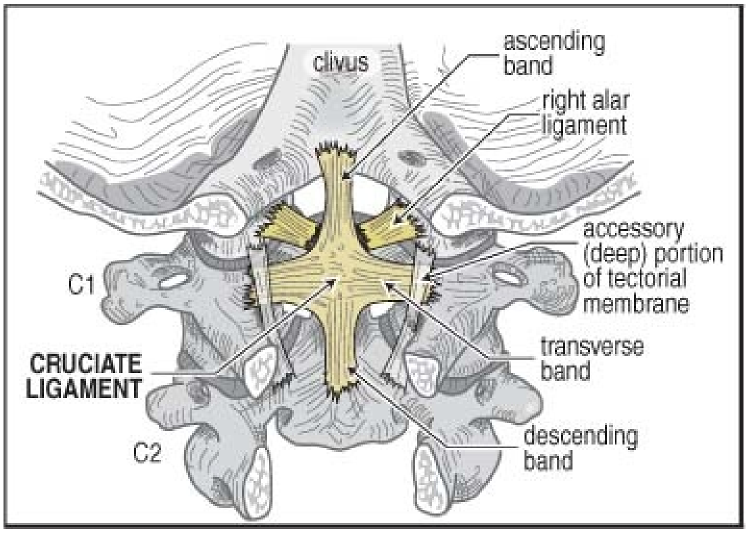

Figure 5-10 Dorsal view of the cruciate and alar ligaments Viewed with tectorial membrane removed. Modified with permission from "In Vitro Cervical Spine Biomechanical Testing" BNI Quarterly, Vol.9, No. 4, 1993

2. ligaments that connect the axis (viz. the odontoid) to the occiput:
   A. **tectorial membrane**: some authors distinguish 2 components
      1. superficial component: cephalad continuation of the posterior longitudinal ligament. A strong band connecting the dorsal surface of the dens to the ventral surface of the FM above, and dorsal surface of C2 & C3 bodies below
      2. accessory (deep) portion: located laterally, connects C2 to occipital condyles
   B. alar ("check") ligaments[19]
      1. occipito-alar portion: connects side of the dens to occipital condyle
      2. atlanto-alar portion: connects side of the dens to the lateral mass of C1
   C. apical odontoid ligament: connects tip of dens to the FM. Little mechanical strength
3. ligaments that connect the axis to the atlas:
   A. **transverse (atlanto-axial) ligament**: the horizontal component of the **cruciate** ligament. Traps the dens against the anterior atlas via a strap-like mechanism (*see Figure 5-11*). Provides the majority of the strength ("the strongest ligament of the spine"[20])
   B. atlanto-alar portion of the alar ligaments (*see above*)
   C. descending band of the cruciate ligament

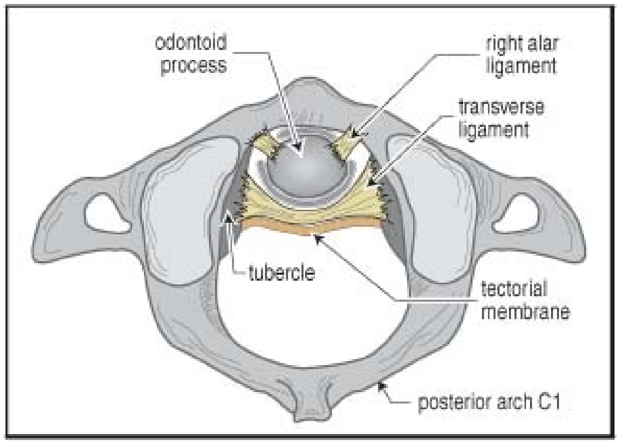

Figure 5-11 C1 viewed from above, showing the transverse and alar ligaments Modified with permission from "In Vitro Cervical Spine Biomechanical Testing" BNI Quarterly, Vol.9, No. 4, 1993

The most important structures in maintaining atlanto-occipital stability are the tectorial membrane and the **alar ligaments**. Without these, the remaining cruciate ligament and apical dentate ligament are insufficient.

5.5. Spinal cord anatomy

5.5.1. Spinal cord tracts

Figure 5-12 depicts a cross-section of a typical spinal cord segment, combining some elements from different levels (e.g. the intermediolateral grey nucleus is only present from T1 to ≈ L1 or L2 where there are sympathetic (thoracolumbar outflow) nuclei). It is schematically divided into ascending and descending halves, however, in actuality, ascending and descending paths coexist on both sides.

Table 5-6 Descending (motor) tracts (↓) in *Figure 5-12*

Number (*see Figure 5-12*)	Path	Function	Side of body
1	anterior corticospinal tract	skilled movement	opposite
2	medial longitudinal fasciculus	?	same
3	vestibulospinal tract	facilitates extensor muscle tone	same
4	medullary (ventrolateral) reticulospinal tract	automatic respirations?	same
5	rubrospinal tract	flexor muscle tone	same
6	lateral corticospinal (pyramidal) tract	skilled movement	same

Table 5-7 Bi-directional tracts in *Figure 5-12*

Number (*see Figure 5-12*)	Path	Function
7	dorsolateral fasciculus (of Lissauer)	
8	fasciculus proprius	short spinospinal connections

Table 5-8 Ascending (sensory) tracts (↑) in *Figure 5-12*

Number (*see Figure 5-12*)	Path	Function	Side of body
9	fasciculus gracilis	joint position, fine touch, vibration	same
10	fasciculus cuneatus		
11	posterior spinocerebellar tract	stretch receptors	same
12	lateral spinothalamic tract	pain & temperature	opposite
13	anterior spinocerebellar tract	whole limb position	opposite
14	spinotectal tract	unknown, ? nociceptive	opposite
15	anterior spinothalamic tract	light touch	opposite

Figure 5-12 also depicts some of the laminae according to the scheme of Rexed. Lamina II is equivalent to the substantia gelatinosa. Laminae III and IV are the nucleus proprius. Lamina VI is located in the base of the posterior horn.

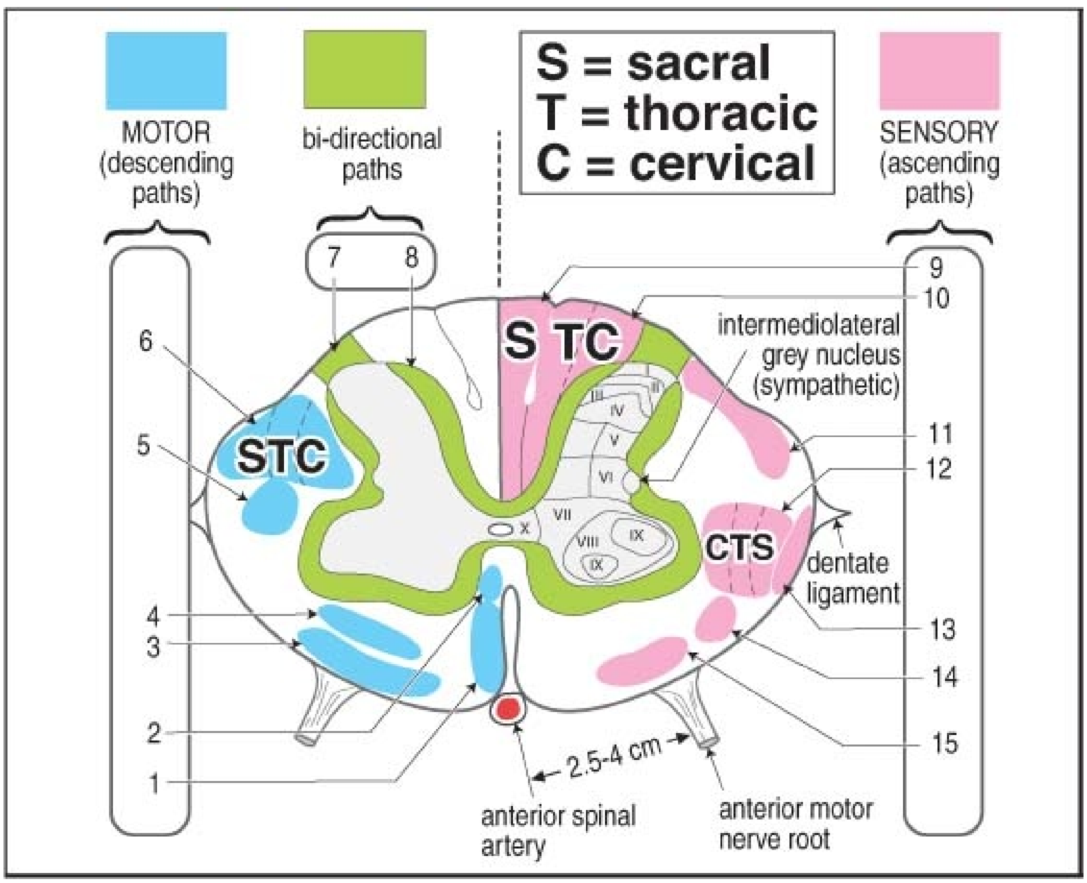

Figure 5-12 Schematic cross-section of cervical spinal cord

SENSATION

PAIN & TEMPERATURE: BODY

Receptors: free nerve endings (probable).

1st order neuron: small, finely myelinated afferents; soma in dorsal root ganglion (no synapse). Enter cord at dorsolateral tract (zone of Lissauer). Synapse: substantia gelatinosa (Rexed II).

2nd order neuron axon cross obliquely in the anterior white commissure ascending ≈ 1-3 segments while crossing to enter the lateral spinothalamic tract.

Synapse: VPL thalamus. 3rd order neurons pass through IC to postcentral gyrus (Brodmann's areas 3, 1, 2).

FINE TOUCH, DEEP PRESSURE & PROPRIOCEPTION: BODY

Fine touch AKA discriminative touch. Receptors: Meissner's & pacinian corpuscles, Merkel's disks, free nerve endings.

1st order neuron: heavily myelinated afferents; soma in dorsal root ganglion (no synapse). Short branches synapse in nucleus proprius (Rexed III & IV) of posterior gray; long fibers enter the ipsilateral posterior columns without synapsing (below T6: fasciculus gracilis; above T6: fasciculus cuneatus).

Synapse: nucleus gracilis/cuneatus (respectively), just above pyramidal decussation. 2nd order neuron axons form internal arcuate fibers, decussate in lower medulla as **medial lemniscus**.

Synapse: VPL thalamus. 3rd order neurons pass through IC primarily to postcentral gyrus.

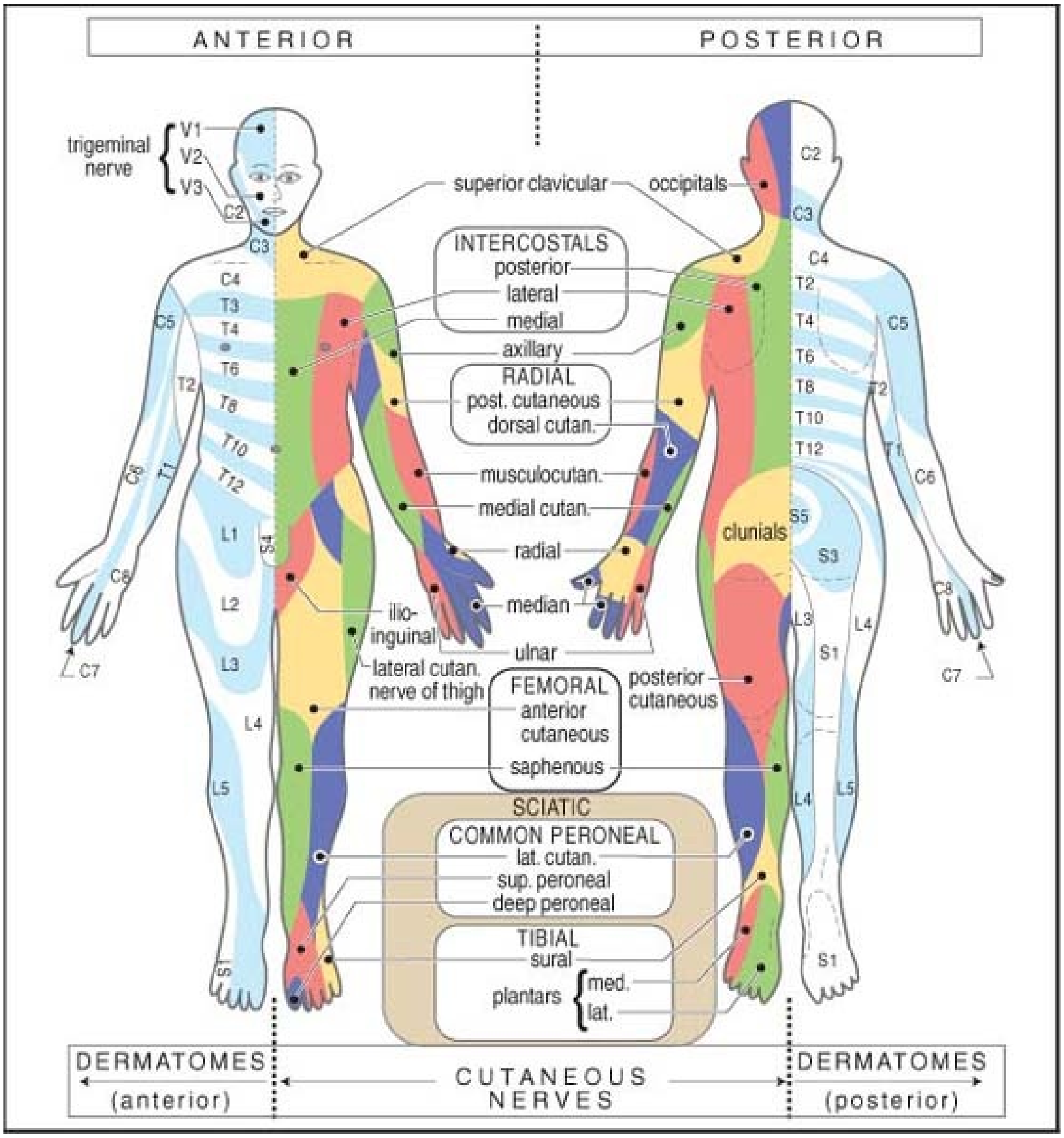

Figure 5-13 Dermatomal and sensory nerve distribution
(Redrawn from "Introduction to Basic Neurology", by Harry D. Patton, John W. Sundsten, Wayne E. Crill and Phillip D. Swanson, © 1976, pp 173, W. B. Saunders Co., Philadelphia, PA, with permission)

LIGHT (CRUDE) TOUCH: BODY

Receptors: as fine touch (*see above*), also peritrichial arborizations.

1st order neuron: large, heavily myelinated afferents (Type II); soma in dorsal root ganglion (no synapse). Some ascend uncrossed in post. columns

(with fine touch); most synapse in Rexed VI & VII.

2nd order neuron axons cross in anterior white commissure (a few don't cross); enter anterior spinothalamic tract.

Synapse: VPL thalamus. 3rd order neurons pass through IC primarily to postcentral gyrus.

5.5.2. Dermatomes and sensory nerves

Figure 5-13 shows anterior and posterior view, each schematically separated into sensory dermatomes (segmental) and peripheral sensory nerve distribution.

5.5.3. Spinal cord vasculature

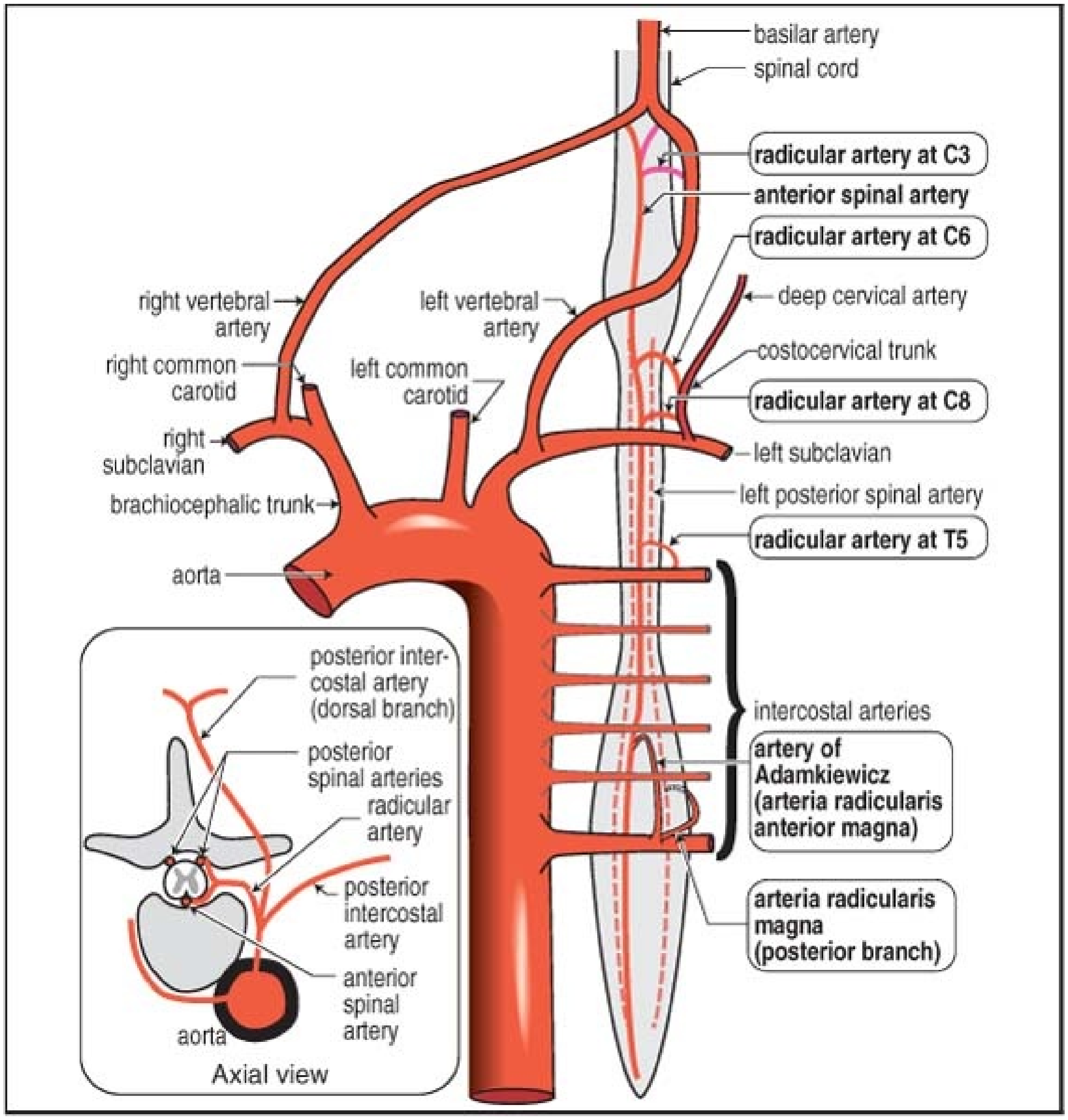

Figure 5-14 Schematic diagram of spinal cord arterial supply
Modified from **Diagnostic Neuroradiology**, 2nd ed., Volume II, pp. 1181, Taveras J M, Woods EH, editors, © 1976, the Williams and Wilkins Co., Baltimore, with permission)

Although a radicular artery from the aorta accompanies the nerve root at many levels, most of these contribute little flow to the spinal cord itself. The anterior spinal artery is formed from the junction of two branches, each from one of the vertebral arteries. Major contributors of blood supply to the anterior spinal cord is from 6-8 radicular arteries at the following levels ("radiculomedullary arteries", the levels listed are fairly consistent, but the side varies[21] (p 1180-1)):

- C3 - arises from vertebral artery
- C6 - usually arises from deep cervical artery } ≈ 10% of population lack an

anterior radicular artery in lower cervical spine[22]

- C8 - usually from costocervical trunk } ≈ 10% of population lack an anterior radicular artery in lower cervical spine[22]
- T4 or T5
- **artery of Adamkiewicz** AKA arteria radicularis anterior magna
  A. the main arterial supply for the spinal cord from ≈ T8 to the conus
  B. located on the left in 80%[23]
  C. situated between T9 & L2 in 85% (between T9 & T12 in 75%); in remaining 15% between T5 & T8 (in these latter cases, there may be a supplemental radicular artery further down)
  D. usually fairly large, gives off cephalic and caudal branch (latter is usually larger) giving a characteristic hair-pin appearance on angiography

The paired posterior spinal arteries are less well defined than the anterior spinal artery, and are fed by 10-23 radicular branches.

The midthoracic region has a tenuous vascular supply (“watershed zone”), possessing only the above noted artery at T4 or T5. It is thus more susceptible to vascular insults.

ANATOMIC VARIANTS

Arcade of Lazorthes: normal variant where the anterior spinal artery joins with the paired posterior spinal arteries at the conus medullaris.

5.6. Cerebrovascular anatomy

5.6.1. Cerebral vascular territories

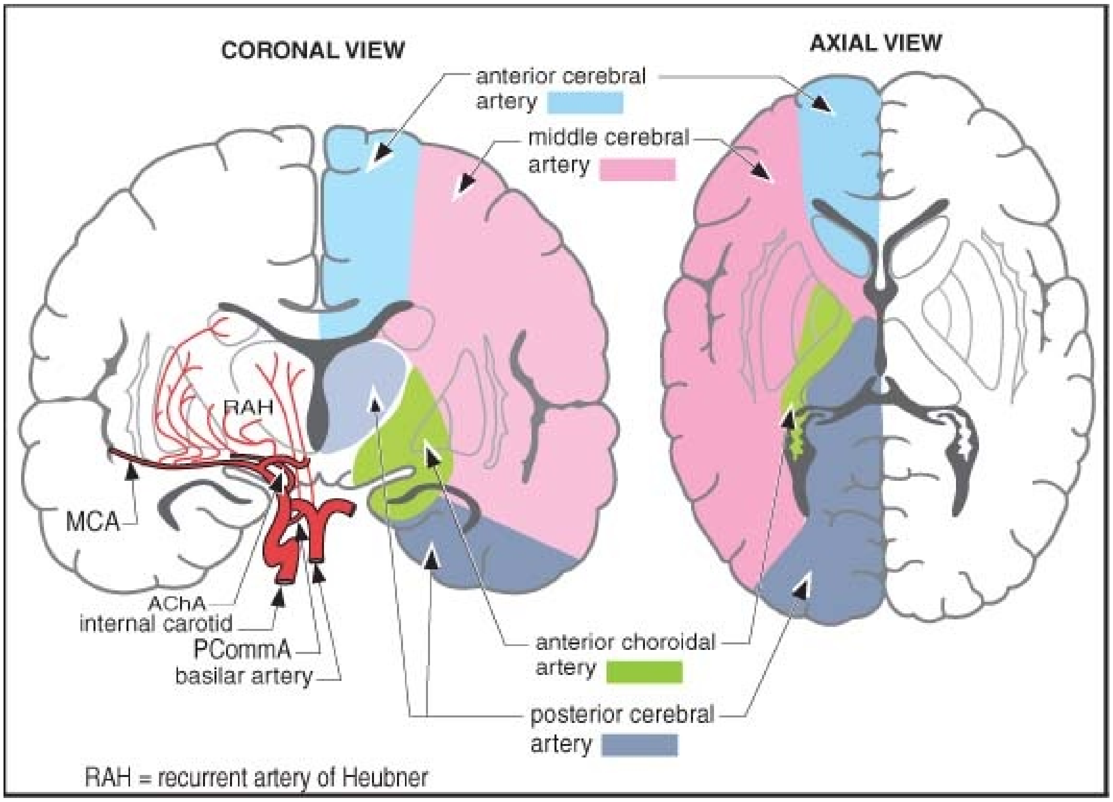

Figure 5-15 Vascular territories of the cerebral hemispheres

Figure 5-15 depicts approximate vascular distributions of the major cerebral arteries. There is considerable variability of the major arteries[24] as well as the central distribution. The lenticulostriates may have origins off of different segments of the middle or anterior cerebral artery). Recurrent artery of Heubner **(RAH)** (AKA medial striate artery) origin: junction of the ACA and a-comm in 62.3%, proximal A2 in 23.3%, A1 in 14.3%[25].

5.6.2. Cerebral arterial anatomy

The symbol "⇒" is used to denote a region supplied by the indicated artery. See *Angiography (cerebral)* on page 134 for angiographic diagrams of the following anatomy.

CIRCLE OF WILLIS

A balanced configuration of the Circle of Willis is present in only 18% of the population. Hypoplasia of 1 or both p-comms occurs in 22-32%, absent or

hypoplastic A1 segments occurs in 25%.

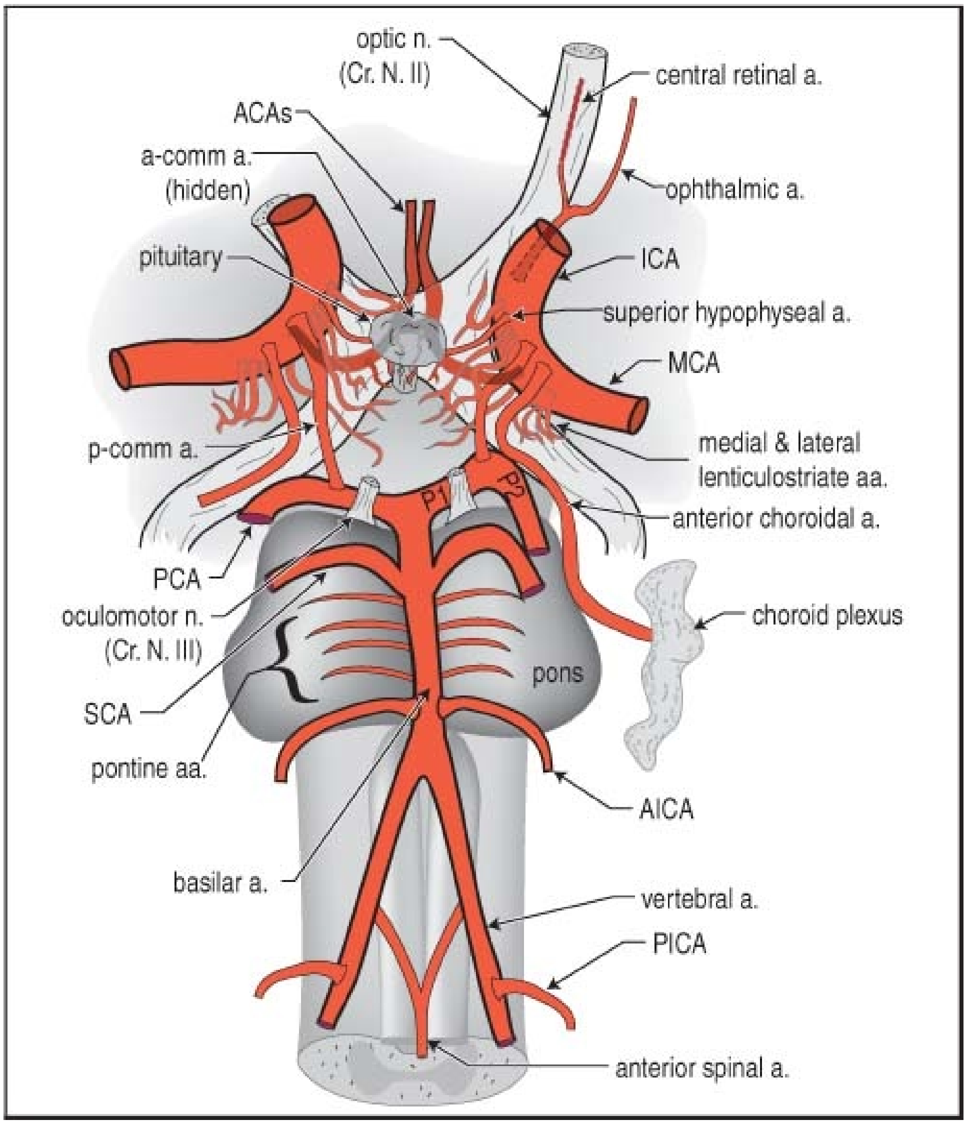

Figure 5-16 Circle of Willis viewed from in front of and below the brain

Key point: the anterior cerebral arteries pass over the superior surface of the optic chiasm.

Anatomical segments of intracranial cerebral arteries

- carotid artery: the traditional numbering system[26] was from rostral to caudal (counter to the direction of flow, and to the numbering scheme of the other arteries). A number of systems have been described to addresses this inconsistency and also to identify anatomically important segments of the

ICA that were not originally delineated (e.g. *see Table 5-9*[27]). Also *see below* for more detail

- anterior cerebral[28]:
  - A1: ACA from origin to ACoA
  - A2: ACA from ACoA to branch-point of callosomarginal
  - A3: from branch-point of callosomarginal to superior surface of corpus callosum 3 cm posterior to the genu
  - A4: pericallosal
  - A5: terminal branch
- middle cerebral[28]:
  - M1: MCA from origin to bifurcation (horizontal segment on AP angiogram). A classical bifurcation into relatively symmetrical superior and inferior trunks is seen in 50%, no bifurcation occurs in 2%, 25% have a very proximal branch (middle trunk) arising from the superior (15%) or the inferior (10%) trunk creating a “pseudo-trifurcation”, a pseudo-tetrafurcation occurs in 5%
    1. lateral fronto-orbital and prefrontal branches arise from M1 or superior M2 trunk
    2. precentral, central, anterior and posterior parietal arteries arise from a superior (60%) or middle (25%) or inferior (15%) trunk
    3. the superior M2 trunk does not give any branches to the temporal lobe
  - M2: MCA trunks from bifurcation to emergence from Sylvian fissure
  - M3-4: distal branches
  - M5: terminal branch
- posterior cerebral (PCA) (several nomenclature schemes exist[29, 30]):
  - P1: PCA from the origin to posterior communicating artery (AKA mesencephalic, precommunicating, circular, peduncular, basilar…). The long and short circumflex and thalamoperforating arteries arise from P1
  - P2: PCA from origin of p-comm to the origin of inferior temporal arteries (AKA ambient, postcommunicating, perimesencephalic), P2 traverses the ambient cistern, Hippocampal, anterior temporal, peduncular perforating and medial posterior choroidal arteries arise from P2
  - P3: PCA from the origin of the inferior temporal branches to the origin of the terminal branches (AKA quadrigeminal segment). P3 traverses

the quadrigeminal cistern

- P4: segment after the origin of the parieto-occipital and calcarine arteries, includes the cortical branches of the PCA

Table 5-9 Segments of the ICA

Cincinnati system	System of Fischer
C1 (cervical)	not described
C2 (petrous)	
C3 (lacerum)	C5
C4 (cavernous)	C4 + part of C5
C5 (clinoid)	C3
C6 (ophthalmic)	C2
C7 (communicating)	C1

ANTERIOR CIRCULATION

ANATOMIC VARIANTS

Bovine circulation: the common carotids arise from a common trunk off the aorta.

EXTERNAL CAROTID

1. superior thyroid a.: 1st anterior branch
2. ascending pharyngeal a.
   A. neuromeningeal trunk of the ascending pharyngeal a.: supplies IX, X & XI
   B. pharyngeal branch: usually the primary feeder for jugular foramen tumors (essentially the <u>only</u> cause of hypertrophy of the ascending pharyngeal a.)
3. lingual a.
4. facial a.: branches anastamose with ophthalmic a. (important in collateral flow with ICA occlusion - *see page 1027*)
5. occipital a. ⇒ posterior scalp
6. posterior auricular
7. superficial temporal
   A. frontal branch
   B. parietal branch

8. (internal) maxillary a. - initially within parotid gland
   A. middle meningeal a.
      1. anterior branch
      2. posterior branch
   B. accessory meningeal
   C. inferior alveolar
   D. infraorbital
   E. others: distal branches of which may anastomose with branches of ophthalmic artery in the orbit

INTERNAL CAROTID ARTERY (ICA)
Lies posterior & medial to the external carotid **(ECA)**.

Segments of the ICA and its branches[27]

- **C1 (cervical)**: begins in neck at carotid bifurcation where the common carotid artery divides into internal and external carotids. Travels in carotid sheath with IJV and vagal nerve, encircled with postganglionic sympathetic nerves **(PGSN)**. C1 ends where the ICA enters carotid canal of petrous bone. No branches
- **C2 (petrous)**: still surrounded by PGSNs. Ends at the posterior edge of the foramen lacerum **(f-Lac)** (inferomedial to the edge of the Gasserian ganglion in Meckel's cave). Three divisions:
   A. vertical segment: ICA ascends then bends as the…
   B. **posterior loop**: anterior to cochlea, bends antero-medially becoming the…
   C. horizontal segment: deep and medial to greater and lesser superficial petrosal nerves, anterior to tympanic membrane **(TM)**
- **C3 (lacerum)**: the ICA passes over (but not through) the f-Lac forming the lateral loop. Ascends in the canalicular portion of the f-Lac to juxtasellar position, piercing the dura as it passes the petrolingual ligament to become the cavernous segment. Branches (usually not visible angiographically):
   A. caroticotympanic (inconsistent) ⇒ tympanic cavity
   B. pterygoid (vidian) branch: passes through foramen lacerum, present in only 30%, may continue as artery of pterygoid canal
- **C4 (cavernous)**: covered by vascular membrane lining sinus, still surrounded by PGSNs. Passes anteriorly then supero-medially, bends

posteriorly (**medial loop** of ICA), travels horizontally, and bends anteriorly (part of **anterior loop** of ICA) to anterior clinoid process. Ends at the **proximal dural ring** (incompletely encircles ICA). Many branches, main ones include:

A. meningohypophyseal trunk **(MHT)** (largest & most proximal). 2 causes of a prominent MHT: 1) tumor (usually petroclival meningioma - *see below*), 2) dural AVM (*see page 1109*)
   1. a. of tentorium (AKA **artery of Bernasconi & Cassinari**): the blood supply of petroclival meningiomas
   2. dorsal meningeal a. (AKA dorsal clival a.)
   3. inferior hypophyseal a. (⇒ posterior lobe of pituitary): post-partum occlusion causes pituitary infarcts (Sheehan's necrosis), however, DI is rare because the stalk is spared

B. anterior meningeal a.

C. a. to inferior portion of cavernous sinus (present in 80%)

D. capsular aa. of McConnell (in 30%): supply the capsule of the pituitary[31]

- **C5 (clinoid)**: begins at proximal dural ring, ends at **distal dural ring** (which completely encircles ICA) where the ICA becomes intradural
- **C6 (ophthalmic)**: begins at distal dural ring, ends just proximal to p-comm. Branches:

A. ophthalmic a.: the origin from the ICA is distal to the cavernous sinus in 89% (intracavernous in 8%, absent in 3%[32]) and can vary from 5 mm anterior to 7 mm posterior to the anterior clinoid[31]. Passes through the optic canal into the orbit. Has a characteristic bayonet-like "kink" on lateral angiogram

B. superior hypophyseal a. branches ⇒ anterior lobe of pituitary & stalk (1st branch of supraclinoid ICA)

- **C7 (communicating)**: begins just proximal to p-comm origin, travels between Cr. N. II & III, terminates just below anterior perforated substance where it bifurcates into the ACA & MCA

A. posterior communicating a. (p-comm)
   1. few anterior **thalamoperforators** (⇒ optic tract, chiasm & posterior hypothalamus): see *Posterior circulation* below
   2. plexal segment: enters supracornual recess of temporal horn, ⇒ only this portion of choroid plexus
   3. cisternal segment: passes through crural cistern

B. **anterior choroidal artery** 33: takeoff 2-4 mm distal to p-comm ⇒ (variable) portion of optic tract, medial globus pallidus, genu of internal capsule **(IC)** (in 50%), inferior half of posterior limb of IC, uncus, retrolenticular fibers (optic radiation), lateral geniculate body (see *page 1028* for occlusion syndromes)

Differentiating p-comm from ACh on arteriogram

1. p-comm origin is proximal to that of the anterior choroidal artery **(ACh)**
2. p-comm is usually larger than ACh
3. p-comm usually goes up or down a little, then straight back & usually bifurcates
4. ACh usually has a superior "hump" (plexal point) where it pass through the choroidal fissure to enter the ventricle

- "**Carotid siphon**": not a segment, but a region incorporating the cavernous, ophthalmic and communicating segments. Begins at the posterior bend of the cavernous ICA, and ends at the ICA bifurcation

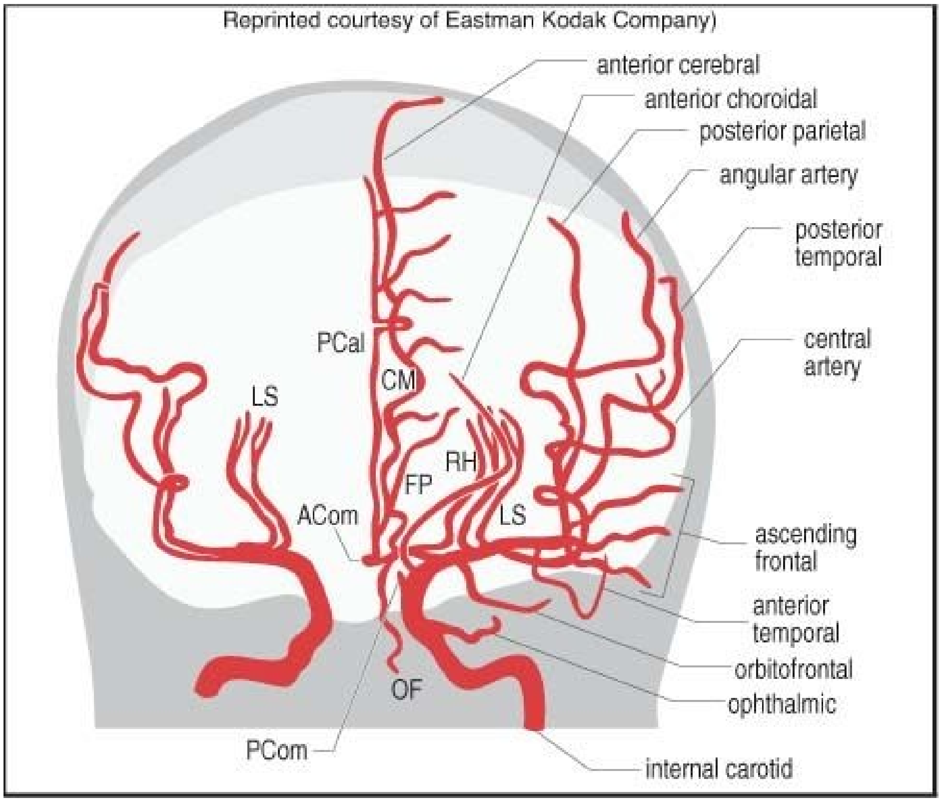

Figure 5-17 Internal carotid arteriogram (AP view)

ANTERIOR CEREBRAL ARTERY (ACA)

Passes between Cr. N. II and anterior perforated substance. See *Figure 5-18*. Branches:

1. recurrent artery (of **Heubner**): 80% arise from A1 (one of the larger

medial lenticulostriates, remainder of lenticulostriates may arise from this artery) ⇒ head of caudate, putamen, and anterior internal capsule

2. medial orbitofrontal artery
3. frontopolar artery
4. callosomarginal
    A. internal frontal branches
        1. anterior
        2. middle
        3. posterior
    B. paracentral artery
5. pericallosal artery (continuation of ACA)
    A. superior internal parietal (precuneate) artery
    B. inferior internal parietal artery

Abbreviations from *Figure 5-17*

ACom	anterior communicating artery
CM	callosomarginal artery
FP	frontopolar artery
LS	lenticulostriate arteries
OF	orbitofrontal artery
PCal	pericallosal artery
PCom	posterior communicating artery
RH	recurrent artery of Heubner

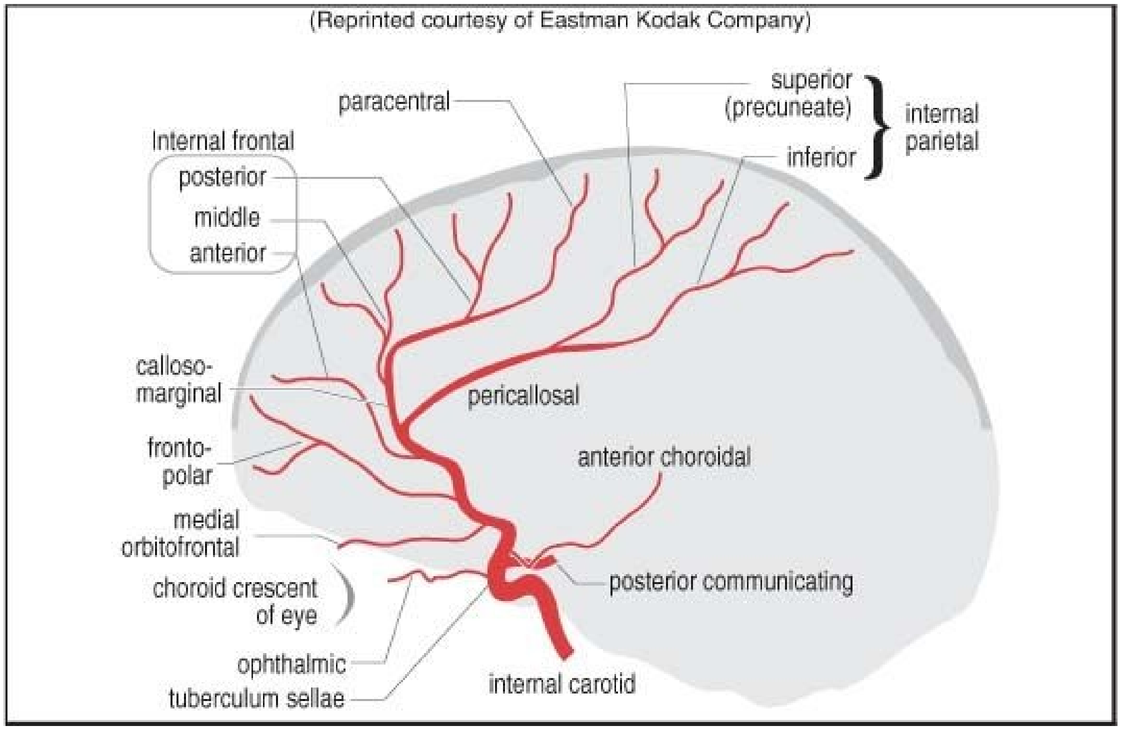

Figure 5-18 Anterior cerebral arteriogram (lateral view)

ANATOMIC VARIANTS

Hypoid: having only one anterior cerebral artery (as in a horse).

MIDDLE CEREBRAL ARTERY (MCA)

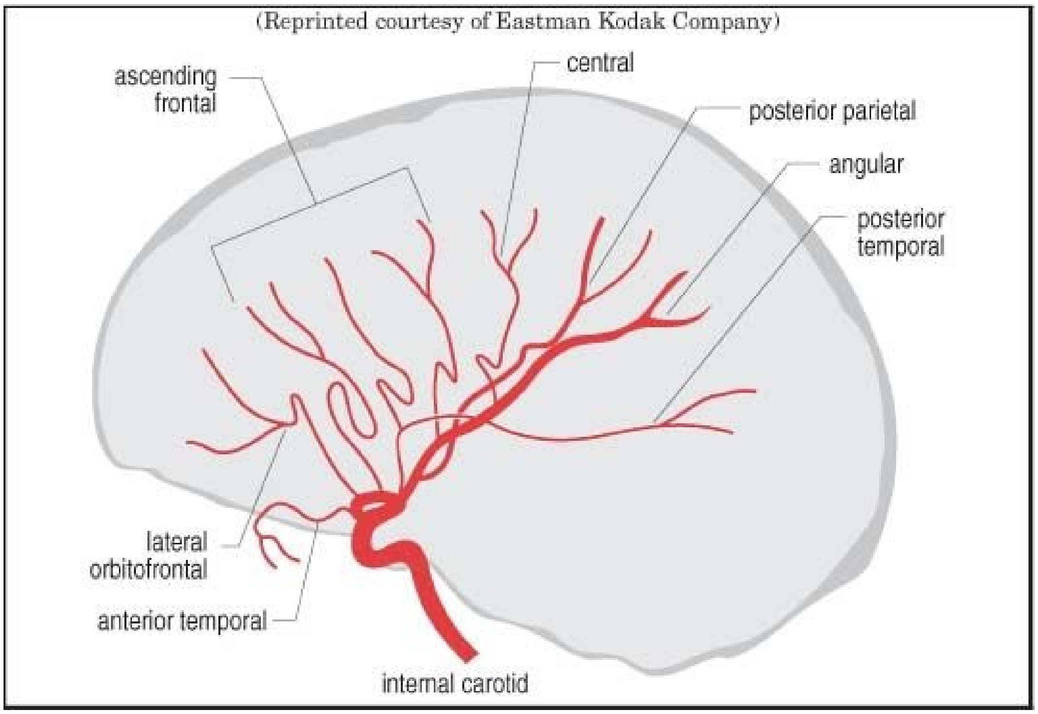

Figure 5-19 Middle cerebral arteriogram (lateral view)

See *Figure 5-19* (*see page 98* for anatomy). Branches vary widely, 10 common ones:

1. medial (3-6 per side) and lateral lenticulostriate arteries
2. anterior temporal
3. posterior temporal
4. lateral orbitofrontal
5. ascending frontal (candelabra)
6. precentral (prerolandic)
7. central (rolandic)
8. anterior parietal (postrolandic)
9. posterior parietal
10. angular

POSTERIOR CIRCULATION

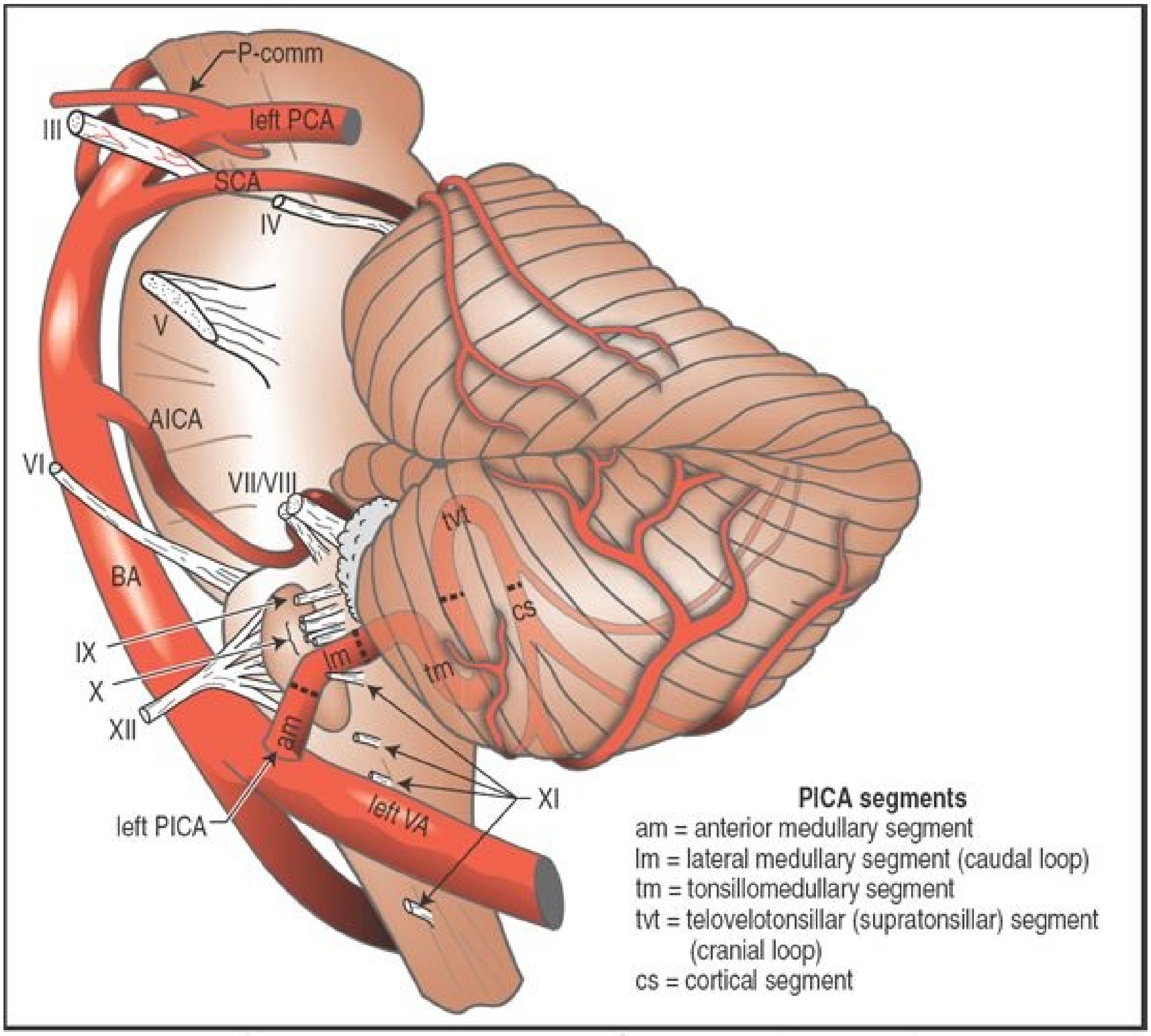

Figure 5-20 Intradural VA and PICA segments (lateral view) Modified with permission from: Lewis SB, Chang DJ, Peace DA, Lafrentz PJ, Day AL. Distal posterior inferior cerebellar artery aneurysms: clinical features and management. J Neurosurg 2002;97(4):756-66.

VERTEBRAL ARTERY (VA)

The VA is the first and usually the largest branch of the subclavian artery. Variant: the left VA arises off the aortic arch in ≈ 4%. Diameter ≈ 3 mm. Mean blood flow ≈ 150 ml/min. The left VA is dominant in 60%. The right VA will be hypoplastic in 10%, and the left will be hypoplastic in 5%. The VA is atretic and does not communicate with the BA on the left in 3%, and on the right in 2% (the VA may terminate in PICA).

Four segments:

V1 prevertebral: from subclavian artery, courses superiorly and posteriorly and enters the foramen transversarium, usually of the 6th vertebral body

V2 ascends vertically within the transverse foramina of the cervical vertebrae surrounded by sympathetic fibers (from the stellate ganglion) and a venous plexus. It is situated anterior to the cervical roots. It turns laterally to enter the foramen within the transverse process of the axis

V3 exits the foramen of the axis and curves posteriorly and medially in a groove on the upper surface of the atlas and enters the foramen magnum

V4 pierces the dura (location somewhat variable) and immediately enters the subarachnoid space. Joins the contralateral VA at the **vertebral confluens** located at the lower pontine border to form the basilar artery **(BA)**

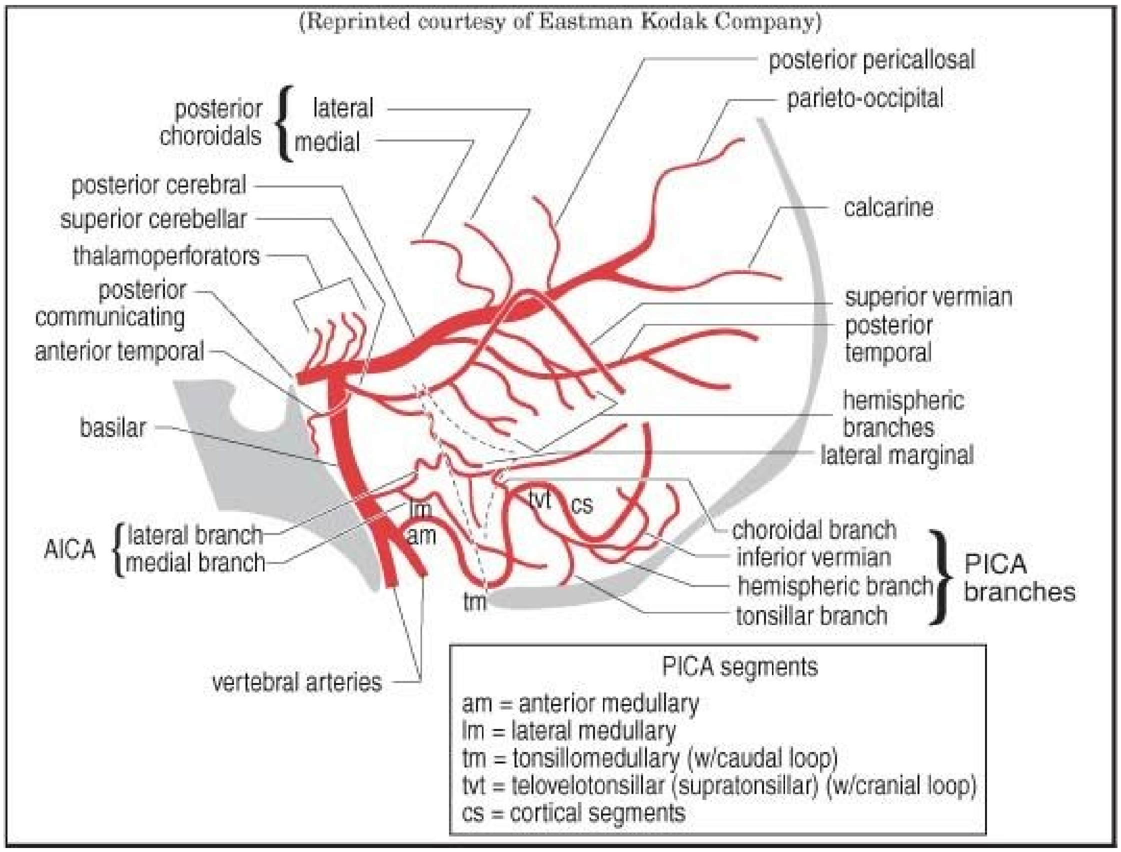

Figure 5-21 Vertebrobasilar arteriogram (lateral view)

Branches:

1. anterior meningeal: arises at body of C_2 (axis), may feed chordomas or foramen magnum meningiomas, may also act as collateral in vascular occlusion
2. posterior meningeal: may a source of blood for some dural AVMs (*see* *page 1109*)
3. medullary (bulbar) aa.

4. posterior spinal
5. posterior inferior cerebellar artery **(PICA)** (largest branch): (*see Figure 5-20*) usually arises ≈10 mm distal to point where VA becomes intradural, ≈ 15 mm proximal to the vertebrobasilar junction
   A. anatomic variants:
      1. in 5-8% the PICA has an extradural origin
      2. "AICA-PICA": origin is off basilar trunk (where AICA would usually originate)
   B. 5 segments[34] (some systems some describe only 4). During surgery, the first three must be preserved, but the last 2 may usually be sacrificed with minimal deficit[35]:
      1. anterior medullary: from PICA origin to inferior olivary prominence. 1 or 2 short medullary short circumflex branches ⇒ ventral medulla
      2. lateral medullary: to origin of nerves IX, X & XI. Up to 5 branches that supply brainstem
      3. tonsillomedullary: to tonsillar midportion (contains caudal loop on angio)
      4. telovelotonsillar (supratonsillar): ascends in tonsillomedullary fissure (contains cranial loop on angio)
      5. cortical segments
   C. 3 branches
      1. **choroidal** a. (BRANCH 1) arises from cranial loop (choroidal point), ⇒ choroid plexus of 4th ventricle
      2. terminal branches:
         a. **tonsillohemispheric** (BRANCH 2)
         b. **inferior vermian** (BRANCH 3) inferior inflection = copular point on angio
6. anterior spinal

ANATOMIC VARIANTS

Fetal circulation: 15-35% of patients supply their posterior cerebral artery on one or both sides from the carotid (via p-comm) instead of via the vertebrobasilar system.

BASILAR ARTERY (BA)

Formed by the junction of the 2 vertebral arteries. Branches:

1. anterior inferior cerebellar artery **(AICA)**: from lower part of BA, runs

postero-laterally anterior to VI, VII & VIII. Often gives off a loop that runs into the IAC and gives off the labyrinthine artery and then emerges to supply the anterolateral inferior cerebellum and then anastomoses with PICA

2. internal auditory (labyrinthine)
3. pontine branches
4. superior cerebellar a. **(SCA)**
   A. sup. vermian
5. **posterior cerebral**: joined by p-comms ≈ 1 cm from origin (the p-comm is the major origin of the PCA in 15% and is termed “fetal” circulation, bilateral in 2%). 3 segments (named for surrounding cistern) and their branches:
   A. peduncular segment (P1)
      1. mesencephalic perforating aa. (⇒ tectum, cerebral peduncles, and these nuclei: Edinger-Westphal, oculomotor and trochlear)
      2. interpeduncular **thalamoperforators** (1st of 2 groups of posterior thalamoperforating aa.)
      3. medial post. choroidal (most from P1 or P2)
      4. “artery of Percheron”: a rare anatomic variant[36] in which a solitary arterial trunk arising from the proximal segment of one PCA supplies the paramedian thalami and rostral midbrain bilaterally
   B. ambient segment (P2)
      1. lateral post. choroidal (most from P2)
      2. thalamogeniculate **thalamoperforators** (2nd of 2 groups of posterior thalamoperforating aa.) ⇒ geniculate bodies + pulvinar
      3. anterior temporal (anastomoses with anterior temporal br. of MCA)
      4. posterior temporal
      5. parieto-occipital
      6. calcarine
   C. quadrigeminal segment (P3)
      1. quadrigeminal & geniculate branches ⇒ quadrigeminal plate
      2. post. pericallosal (splenial) (anastomoses with pericallosal of ACA)

5.6.3. Cerebral venous anatomy

SUPRATENTORIAL VENOUS SYSTEM

See *Figure 5-22*, page 105 for angiogram and branches.

The left and right internal jugular veins **(IJVs)** are the major source of outflow of blood from the intracranial compartment. The right IJV is usually dominant. Other sources of outflow include orbital veins and the venous plexuses around the vertebral arteries. Diploic and scalp veins may act as collateral pathways, e.g. with superior sagittal sinus obstruction[38]. The following outline traces the venous drainage back from the IJVs.

A. inferior petrosal sinus: terminates (i.e. drains to) ≤ 1 cm of junction of sigmoid and transverse sinuses
B. sigmoid sinus
  1. superior petrosal sinus: drains to IJV near junction with sigmoid sinus
  2. transverse sinus (R > L in 65%)
    A. v. of Labbe (inferior anastomotic v.)
    B. confluens of sinuses (torcular herophili)
      1. occipital sinus
      2. superior sagittal sinus
        a. v. of Trolard (superior anastomotic v.): the prominent superficial vein on the non-dominant side (Labbé is more prominent on the dominant side)
      3. straight sinus
        a. inferior sagittal sinus
        b. great cerebral v. (of Galen)
          i. pre-central cerebellar v.
          ii. basal vein of Rosenthal
          iii. internal cerebral v.: joined at the foramen of Monro (venous angle) by:
            1. anterior septal v.
            2. thalamostriate v.

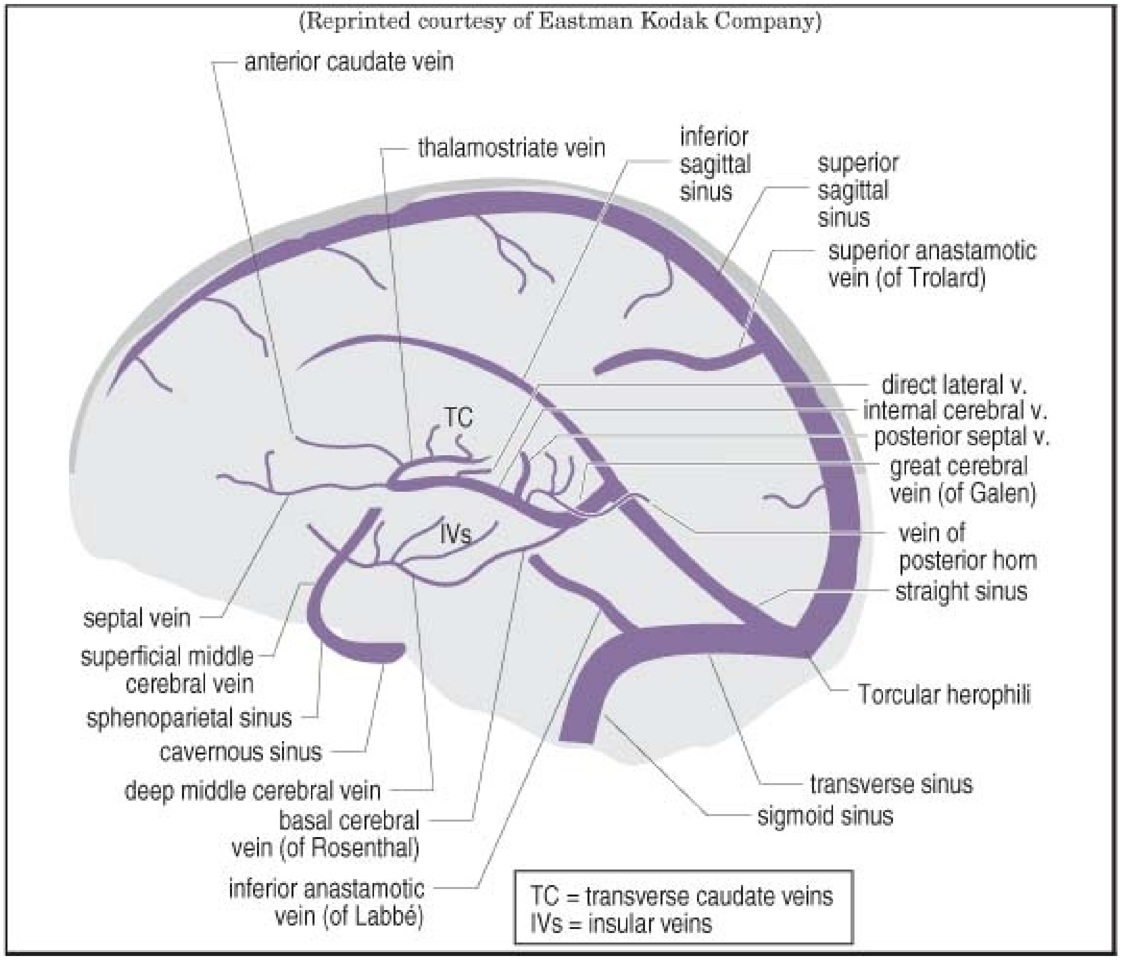

Figure 5-22 Internal carotid venogram (lateral view)

CAVERNOUS SINUS

Although classical teaching depicts the cavernous sinus as a large venous space with multiple trabeculations, injection studies[39] and surgical experience[40] supports the concept of the cavernous sinus as a plexus of veins. It is highly variable between individuals and from side-to-side. *Figure 5-23* is an oversimplified schematic of one section through the right cavernous sinus.

1. inflowing veins:
   - A. superior & inferior ophthalmic veins
   - B. superficial middle cerebral veins
   - C. sphenoparietal sinus
   - D. superior & inferior petrosal sinus
2. outflow:
   - A. sphenoparietal sinus
   - B. superior petrosal sinus

C. basilar plexus (which drains to the inferior petrosal sinus)
D. pterygoid plexus
E. the right and left cavernous sinuses communicate anteriorly and posteriorly via the circular sinus

3. contents[41]
   - **O**culomotor n. (III)
   - **T**rochlear n. (IV)
   - **O**phthalmic division of trigeminal (V1)
   - **M**axillary division of trigeminal (V2): the only nerve of the cavernous sinus that doesn't exit the skull through the superior orbital fissure (it exits through foramen rotundum)
   - **C**arotid artery (ICA). 3 segments within the cavernous sinus
     1. posterior ascending segment: immediately after ICA enters the sinus
     2. horizontal segment: after ICA turns anteriorly (the longest segment of the intracavernous ICA)
     3. anterior ascending segment: ICA turns superiorly
   - **A**bducens n. (VI): the only nerve NOT attached to lateral dural wall, some-times referred to as the only cranial nerve *inside* the cavernous sinus

3. **triangular space** (of Parkinson): superior border formed by Cr. N. III & IV, and the lower margin formed by V_1 & VI (a landmark for surgical entrance to the cavernous sinus)[42, 43 (p 3007)]

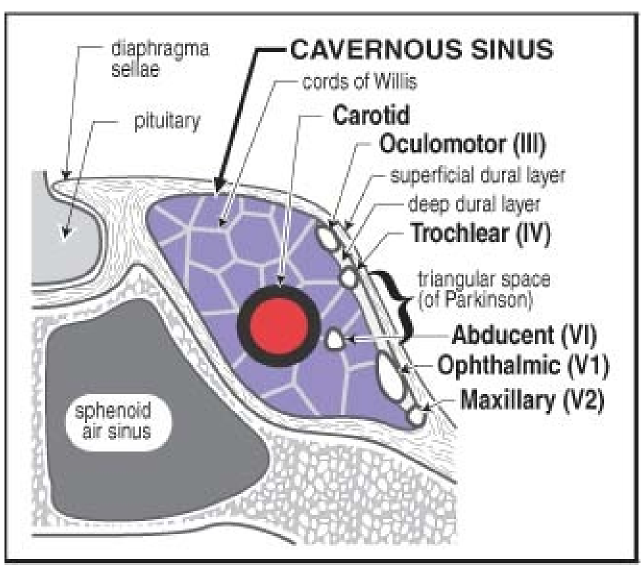

Figure 5-23 Right cavernous sinus (coronal section) Modified from the **Journal of Neurosurgery**,

Umansky F and Nathan H, Vol. 56, pp. 228-34, 1982, with permission)

POSTERIOR FOSSA VENOUS ANATOMY

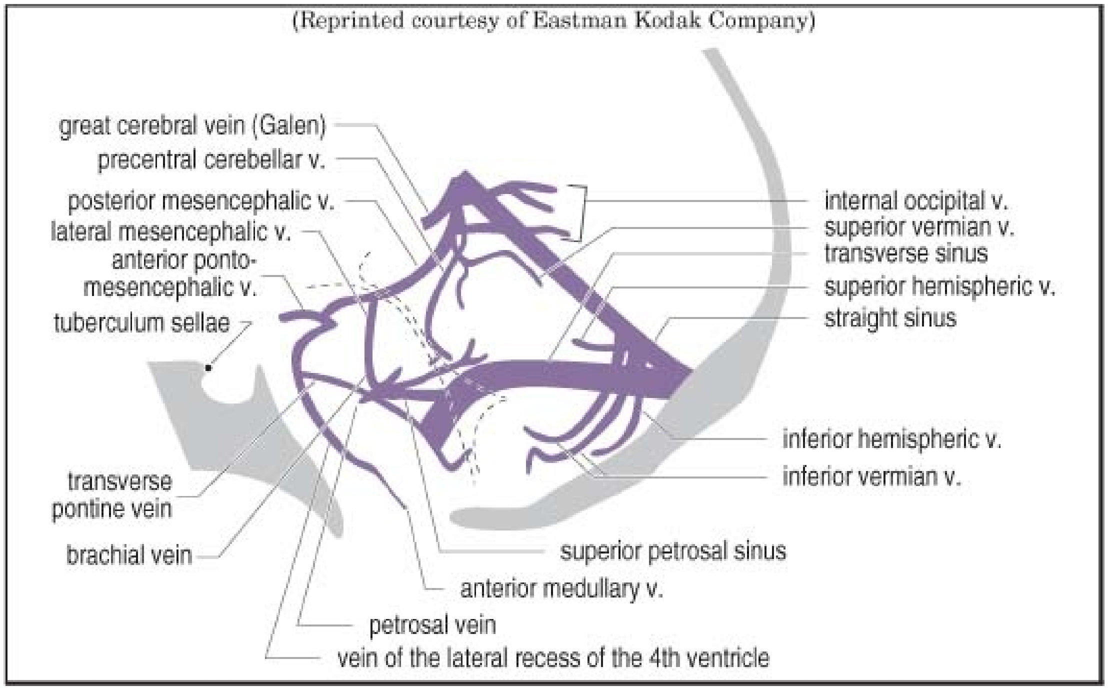

Figure 5-24 Vertebrobasilar venogram (lateral view)

5.6.4. Carotid-vertebrobasilar anastomoses

P-comm artery: the "normal" (most common) anastomosis.

Persistent fetal anastomoses[37]: (*see Figure 5-25*) result from failure to involute as the VAs and p-comms develop (order of involution: otic, hypoglossal, primitive trigeminal, proatlantal). Most are asymptomatic. However, some may be associated with vascular anomalies such as aneurysms or AVMs, and occasionally cranial nerve symptoms (e.g. trigeminal neuralgia with PPTA) can occur.

Four types (from cranial to caudal - the 1st 3 are named for the associated cranial nerve):

1. **persistent primitive trigeminal artery (PPTA)**: seen in ≈ 0.6% of cerebral angiograms. The most common of the persistent fetal anastomoses (83%). May be associated with trigeminal neuralgia (*see page 551*). Connects the cavernous carotid to the basilar artery. Arises from the ICA proximal to the origin of the meningohypophyseal trunk

(50% go through sella, 50% exit the cavernous sinus & course with the trigeminal nerve) and connects to the upper basilar artery between AICA & SCA. The VAs may be small. Saltzman type 1 variant: the p-comms are hypoplastic and the PPTA provides significant blood supply to the distributions of the distal BA, PCA and the SCAs (the basilar artery is often hypoplastic). Saltzman type 2: p-comm supplies PCA. Saltzman type 3: PPTA joins the SCA (instead of the BA). It is critical to recognize a PPTA before doing a Wada test (*see page 421*) because of the risk anesthetizing the brainstem, and in doing transsphenoidal surgery because of risk of arterial injury. May rarely be an explanation of posterior fossa symptoms in a patient with carotid disease

2. **otic**: the first to involute, and the rarest to persist (8 cases reported). Passes through IAC to connect petrous carotid to basilar artery
3. **hypoglossal**: connects petrous or distal cervical ICA (origin usually between C1-C3) to VA. Traverses the hypoglossal canal. Does not cross foramen magnum
4. **proatlantal intersegmental**: connects cervical ICA to VA. May arise from: bifurcation of common carotid, ECA, or ICA from C2-C4. Anastomosis with VA in suboccipital region. 50% have hypoplastic proximal VA. 40 cases reported

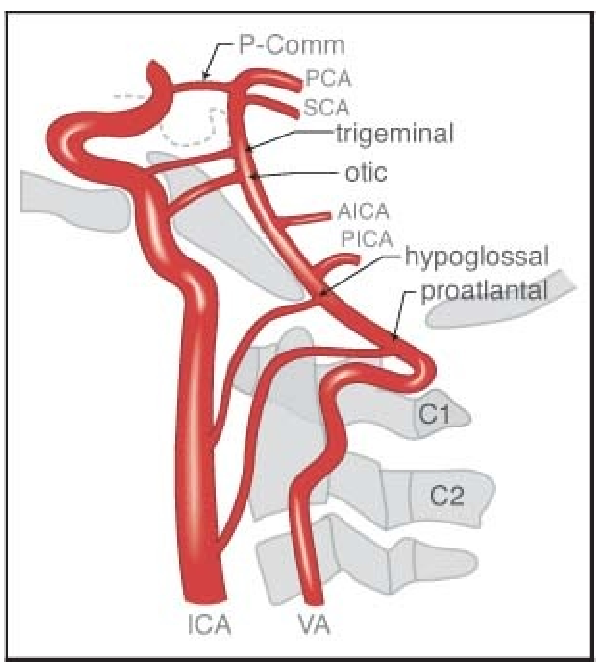

Figure 5-25 Carotid-vertebrobasilar anastomoses

5.7. Internal capsule

For a schematic diagram, *see Figure 5-26*. *Table 5-10* delineates the thalamic sub-radiations. Most IC lesions are caused by vascular accidents (thrombosis or hemorrhage).

Vascular supply of the internal capsule (IC)

1. anterior choroidal: ⇒ all of retrolenticular part (includes optic radiation) and ventral part of posterior limb of IC
2. lateral striate branches (AKA capsular branches) of middle cerebral artery: ⇒ most of anterior AND posterior limbs of IC
3. genu usually receives some direct branches of the internal carotid artery

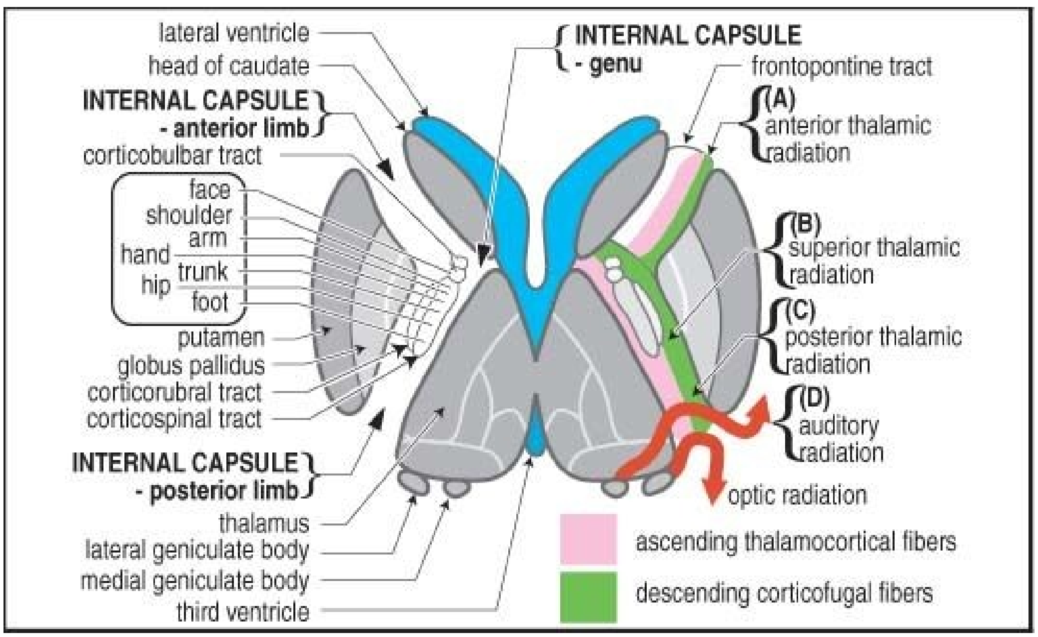

Figure 5-26 Internal capsule schematic diagram (left side shows tracts, right side shows radiations)

Table 5-10 Four Thalamic "subradiations" (AKA thalamic peduncles)
(labeled A-D in *Figure 5-26*)

Radiation	Connection			Comments
anterior (**A**)	medial & anterior thalamic nucleus	↔	frontal lobe	
superior (**B**)	rolandic areas	↔	ventral thalamic nuclei	general sensory fibers from body & head to terminate in postcentral gyrus (areas 3,1,2)
posterior (**C**)	occipital & posterior parietal	↔	caudal thalamus	
inferior (**D**)	transverse temporal gyrus of Heschl	↔	MGB	(small) includes auditory radiation

5.8. Miscellaneous

Obersteiner-Redlich zone (ORZ)

Transition from CNS myelin to peripheral myelin of cranial nerves = area where pressure from intracranial structures can cause cranial nerve symptoms (trigeminal neuralgias, hemifacial spasm, disabling positional vertigo, etc.)[44]. Also, zone where neoplasms tend to occur, especially vestibular schwannoma. On Cr. N. VIII, the ORZ is 8-12 mm distal to exit point from brainstem, and is close to porus acusticus (especially common on vestibular division)[14 (p 695)].

Dentate ligament

The dentate ligament separates dorsal from ventral nerve roots in the spinal nerves. The spinal accessory nerve (Cr. N. XI) is dorsal to the dentate ligament.

5.9. Neurophysiology

5.9.1. Blood-brain barrier

The passage of water-soluble substances from the blood to the CNS is limited by tight junctions (zonulae occludentes) which are found between cerebral capillary endothelial cells, limiting penetration of the cerebral parenchyma (blood-brain barrier, **(BBB)**), as well as between choroid plexus epithelial cells (blood-CSF barrier)[45]. A number of specialized mediated transport systems allow transmission of, among other things, glucose and certain

amino acids (especially precursors to neurotransmitters).

The efficacy of the BBB is compromised in certain pathological states (e.g. tumor, infection, trauma, stroke, hepatic encephalopathy…), and can also be manipulated pharmacologically (e.g. hypertonic mannitol increases the permeability, whereas steroids reduce the penetration of small hydrophilic molecules).

The BBB is absent in the following areas: choroid plexus, hypophysis, tuber cinereum, area postrema, pineal and preoptic recess.

CEREBRAL EDEMA

Three basic types (diffusion-weighted MRI may be able to differentiate, *see page 132*):

1. **cytotoxic**: BBB is closed, therefore no protein extravasation, therefore no enhancement on CT or MRI. Cells swell then shrink. Seen e.g. in head injury
2. **vasogenic**: BBB disrupted. Protein (serum) leaks out of vascular system, and therefore may enhance on imaging. Extracellular space **(ECS)** expands. Cells are stable. Responds to corticosteroids (e.g. dexamethasone). Seen e.g. surrounding metastatic brain tumor
3. **ischemic**: a combination of the above. BBB closed initially, but then may open. ECS shrinks then expands. Fluid extravasates late. May cause delayed deterioration following intracerebral hemorrhage (*see page 1125*)

5.9.2. Pituitary embryology & neuroendocrinology

The **posterior pituitary** (neurohypophysis) derives from downward evagination of neural crest cells (brain neuroectoderm) from the floor of the third ventricle. The residual recess in the floor of the third ventricle is called the median eminence. The **anterior pituitary** gland (adenohypophysis) develops from an evagination of epithelial ectoderm of the oropharynx, the evagination is known as Rathke's pouch and is eventually separated from the oropharynx by the sphenoid bone. Cleft-like remnants of Rathke's pouch separates the adenohypophysis and neurohypophysis. The adenohypophysis is comprised of the pars distalis (anterior lobe), the pars intermedia (intermediate lobe) and the pars tuberalis (extension of adenohypophyseal cells on the anterior aspect of the pituitary stalk). The pituitary gland is functionally <u>outside</u> the blood-brain barrier.

PITUITARY HORMONES AND THEIR CONTROLS

The pituitary gland releases 8 hormones, 6 from the anterior pituitary, 2 from the posterior pituitary (*see Figure 5-27*). The anterior pituitary is one of only two sites in the body having a portal circulation (the other being the liver). 6 hypothalamic hormones released in a pulsatile fashion are conveyed in blood from hypothalamic capillaries through this portal circulation via the pituitary stalk to a second capillary bed in the anterior pituitary where they control release of hormones by adenohypophyseal gland cells.

Hormones released from the posterior pituitary (ADH & oxytocin) are synthesized in <u>neurons</u> in the hypothalamus (<u>not</u> gland cells) and are conveyed along their <u>axons</u> also in the pituitary stalk to the posterior pituitary gland where they are released.

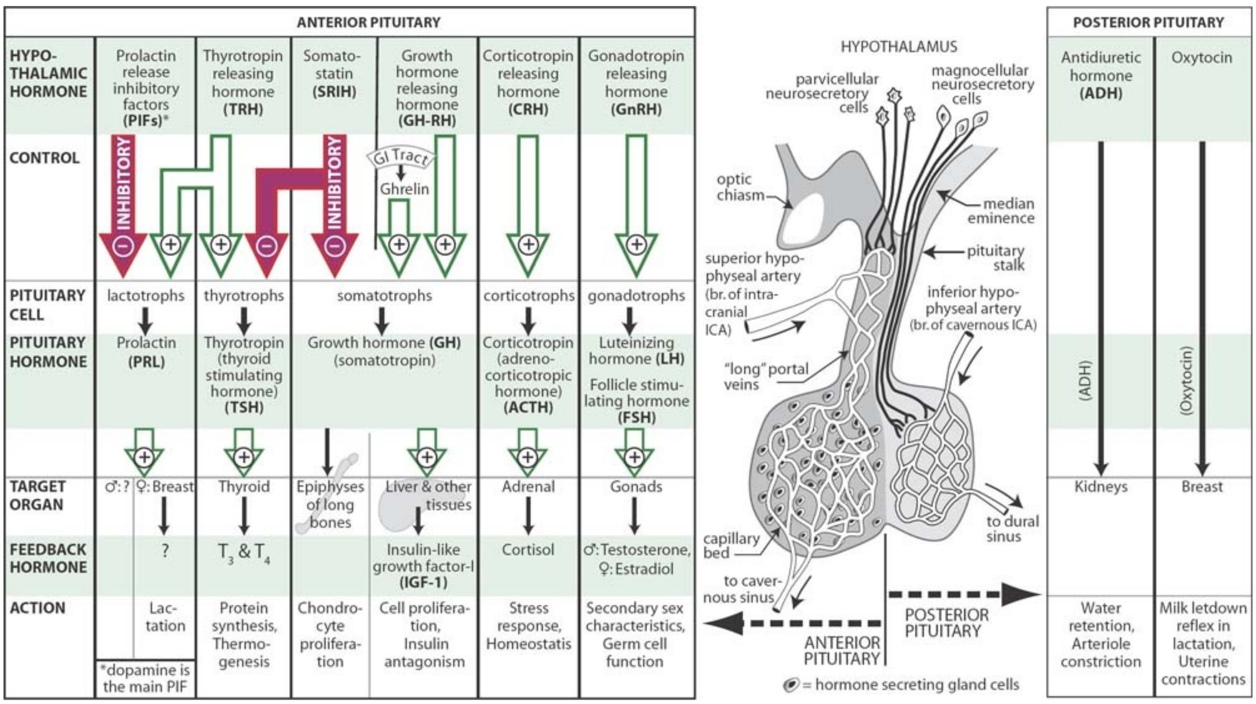

Figure 5-27 Pituitary neuroendocrinology

The complete homeostatic loop (including negative feedback of the hypothalamic hormones) will not be covered here, and the reader is referred to physiology texts.

Propiomelanocortin (POMC) AKA proopiomelanocortin

241 amino acid polypeptide hormone precursor synthesized primarily in

corticotroph cell of the anterior pituitary (but also found in the hypothalamus). Contains amino acid sequences for ACTH, alpha–melanocyte–stimulating hormone **(α-MSH)**, ß-lipotropin, γ-lipotropin, ß-endorphin and met-enkephalin.

Corticotropin AKA adrenocorticotrophic hormone (ACTH)

A 39 amino acid trophic hormone synthesized from POMC (*see above*). The first 13 amino acids at the amino terminal of ACTH are identical to α-MSH. Active half-life is ≈ 10 minutes. Produces a diurnal peak in cortisol (the highest peak occurs in the early morning, with a second, lesser peak in the late afternoon) and also increases in response to stress.

Control: CRH from the hypothalamus stimulates the release of ACTH.

Prolactin (PRL)

AKA somatomammotropin. 199 amino-acid protein weighing 23,000 daltons. Levels are higher in females than males, and are higher still in pregnancy (*see page 643*). Secreted in pulsatile fashion with a frequency and amplitude that varies during menstrual cycle (range: 5-27 ng/ml). There is also diurnal variation: levels begin to rise 1 hour after the onset of sleep, peak ≈ 5:00-7:00 AM, and nadir in midmorning after awakening. Heterogeneity of the molecule may produce different results between bioassays and immunoassays.

Control: PRL is the only pituitary hormone predominantly under inhibitory control from the hypothalamus by prolactin inhibitory factors **(PRIFs)**, with dopamine being the primary PRIF. Prolactin releasing factors **(PRFs)** include: thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP). The physiologic role of PRFs is not established. For differential diagnosis of hyperprolactinemia *see page 644*.

Growth hormone (GH)

A 191 amino-acid polypeptide trophic hormone. GH normally has pulsatile secretion (≈ 5-10 pulses/24 hours, primarily at night, up to 30 μg/L), levels may be undetectable (< 0.2 μg/L) by standard assays between pulses[46]. Insulin-like growth factor-1 **(IGF-1)** (formerly AKA somatomedin-C) is the protein secreted primarily by the liver in response to GH that is responsible for most of GH's systemic effects (*see page 648* for levels). GH also acts directly on epiphyseal end-plates of long bone to stimulate chondrocyte proliferation.

Control: GH is under dual hypothalamic control via the hypophysial portal system. GH-releasing hormone **(GHRH)** from the arcuate nucleus stimulates pituitary secretion and synthesis of GH and induces GH gene transcription. **Somatostatin** from the periventricular nucleus suppresses GH release only. GH release is also stimulated by **ghrelin**[47], a peptide synthesized primarily in the GI tract in response to certain nutrients (may act partially or totally via hypothalamic GHRH).

Thyrotropin AKA thyroid stimulating hormone (TSH)

Glycoprotein trophic hormone secreted by thyrotroph cells of the anterior pituitary.

Control: TSH is also under dual hypothalamic control. TRH stimulates production and release of TSH. Somatostatin inhibits the release of TSH.

Gonadotropins

Follicle stimulating hormone **(FSH)** and leuteinizing hormone **(LH)** (AKA lutropin) are released from the pituitary in response to gonadotropin releasing hormone 1 **(GnRH)** (formerly leuteinizing hormone releasing hormone **(LH-RH)**) synthesized primarily in the preoptic area of the hypothalamus.

Antidiuretic hormone (ADH)

AKA arginine vasopressin **(AVP)**. The major source of this nanopeptide hormone is the magnocellular portion of the supraoptic nucleus of the hypothalamus. It is conveyed along axons in the supraoptic-hypophyseal tract to the posterior pituitary gland where it is released into the systemic circulation. All actions of ADH result from binding of the hormone to specific membrane bound receptors on the surface of target cells[48]. One of the major effects of ADH is to increase the permeability of the distal renal tubules resulting in increased reabsorption of water, diluting the circulating blood and producing a concentrated urine. The most powerful physiologic stimulus for ADH release is an increase in serum osmolality, a less potent stimulus is a reduction of intravascular volume. ADH is also released in glucocorticoid deficiency, and is inhibited by exogenous glucocorticoids and adrenergic drugs. ADH is also a potent vasoconstrictor.

Oxytocin

A nonapeptide. The hypothalamus is the main source of pituitary oxytocin which is stored in nerve endings in the neurohypophysis and is involved in the milk letdown reflex for breastfeeding as well as in uterine contraction during labor.

5.9.3. Regional brain syndromes

This section serves to briefly describe typical syndrome associated with lesions in various areas of the brain. Unless otherwise noted, lesions considered are destructive.

1. frontal lobe
   A. unilateral injury:
      1. may produce few clinical findings except with very large lesions
      2. bilateral or large unilateral lesions: apathy, abulia
      3. the frontal eye field (for contralateral gaze) is located in the posterior frontal lobe (Br. area 8, shown as the striped area in *Figure 5-1*, page 84). Destructive lesions impair gaze to the contralateral side (patient looks towards the side of the lesion), whereas irritative lesions (i.e. seizures) cause the center to activate, producing contralateral gaze (patient looks away from the side of the lesion). Also *see page 834*
   B. bilateral injury: may produce apathy, abulia
   C. olfactory groove region: may produce Foster Kennedy syndrome (*see below*)
   D. prefrontal lobes control "executive function": planning, prioritizing, organizing thoughts, suppressing impulses, understanding the consequences of decisions
2. parietal lobe: major features (*see below* for details)
   A. either side: cortical sensory syndrome, sensory extinction, contralateral homonymous hemianopia, contralateral neglect
   B. *dominant* parietal lobe lesion (left in most): language disorders (aphasias), Gerstmann's syndrome (*see page 113*), bilateral astereognosis
   C. *non-dominant* parietal lobe lesions: topographic memory loss, anosognosia and dressing apraxia
3. occipital lobe: homonymous hemianopsia
4. cerebellum

A. lesions of the cerebellar *hemisphere* cause ataxia in the ipsilateral limbs

B. lesions of the cerebellar vermis cause truncal ataxia

5. brainstem: usually produces a mixture of cranial nerve deficits and long tract findings (*see below* for some specific brainstem syndromes)
6. pineal region

A. Parinaud's syndrome: *see page 114*

FOSTER KENNEDY SYNDROME

Usually from olfactory groove or medial third sphenoid wing tumor (usually meningioma). Now rare due to earlier detection by CT scan. Classic triad:

1. ipsilateral anosmia
2. ipsilateral central scotoma (with optic atrophy due pressure on optic nerve)
3. contralateral papilledema (from elevated ICP)

Occasionally ipsilateral proptosis will also occur due to orbital invasion of tumor.

5.9.3.1. Parietal lobe syndromes[49] (p 308-12)

PARIETAL LOBE ANATOMY

The parietal lobe is located behind the central sulcus, above the Sylvian fissure, merging posteriorly into the occipital lobe (the border on the medial surface of brain is defined by a line connecting the parieto-occipital sulcus to the pre-occipital notch).

PARIETAL LOBE NEUROPHYSIOLOGY

- either side: anterior parietal cortex organizes tactile precepts (probably contralateral) and integrates with visual and auditory sensation to build awareness of body and its spatial relations
- dominant side (on left in 97% of adults): understanding language, includes "cross-modal matching" (auditory-visual, visual-tactile, etc.). Dysphasia present with dominant lobe lesions often impedes assessment
- non-dominant side: integrates visual and proprioceptive sensation to allow manipulation of body and objects, and for certain constructional activities

CLINICAL SYNDROMES OF PARIETAL LOBE DISEASE

1. <u>unilateral</u> parietal lobe disease (dominant or non-dominant):
   A. cortical sensory syndrome (*see below*) and sensory extinction (neglecting 1 of 2 simultaneously presented stimuli). Large lesion → hemianesthesia
   B. congenital injury → mild hemiparesis & contralateral muscle atrophy
   C. homonymous hemianopia or visual inattentiveness
   D. occasionally: anosognosia
   E. neglect of contralateral half of body and visual space (more common with right side lesions)
   F. abolition of <u>optokinetic nystagmus</u> to one side
2. additional effects of *dominant* parietal lobe lesion (left in most):
   A. language disorders (aphasias)
   B. speech-related or verbally mediated functions, e.g. cross-modal matching (e.g. patient understands spoken words and can read, but cannot understand sentences with elements of relationships)
   C. **Gerstmann's syndrome**, classically:
      1. agraphia without alexia (patients can read but cannot write)
      2. left-right confusion
      3. digit agnosia: inability to identify finger by name
      4. acalculia
   D. tactile agnosia (bilateral astereognosis)
   E. bilateral ideomotor apraxia (inability to carry out verbal commands for activities that can otherwise be performed spontaneously with ease)
3. additional effects of *non-dominant* parietal lobe lesions (usually right):
   A. topographic memory loss
   B. anosognosia and dressing apraxia

CORTICAL SENSORY SYNDROME

Lesion of postcentral gyrus, especially area that maps to hand.

- sensory deficits:
  A. loss of position sense and of passive movement sense
  B. inability to localize tactile, thermal, and noxious stimuli
  C. astereognosis (inability to judge object size, shape, and identity by feel)
  D. agraphesthesia (cannot interpret numbers written on hand)
  E. loss of two point discrimination
- preserved sensations: pain, touch, pressure, vibration, temperature

• other features
    A. easy fatigability of sensory perceptions
    B. difficulty distinguishing simultaneous stimulations
    C. prolongation of superficial pain with hyperpathia
    D. touch hallucinations

ASOMATAGNOSIAS

ANTON-BABINSKI SYNDROME

Unilateral asomatagnosia. May seem more common with non-dominant (usually right) parietal lesions because it may be obscured by the aphasia that occurs with dominant (left) sided lesions.

1. anosognosia (indifference or unawareness of deficits, patient may deny that paralyzed extremity is theirs)
2. apathy (indifference to failure)
3. allocheiria (one-sided stimuli perceived contralaterally)
4. dressing apraxia: neglect of one side of body in dressing and grooming
5. extinction: patient is unaware of contralateral stimulus when presented with double-sided simultaneous stimulation
6. inattention to an entire visual field (with or without homonymous hemianopia), with deviation of head, eyes, and torsion of body to unaffected side

APHASIAS

As related to parietal lobe lesions:

1. **Wernicke's aphasia**: lesion of auditory association areas or their separation from angular gyrus and primary auditory cortex. A fluent aphasia (normal sentence length & intonation, devoid of meaning). May include paraphasias. Lesion in region of Wernicke's area (Brodmann areas 40 & 39, see *Figure 5-1*, page 84)
2. **Broca's (motor) aphasia**: in reality, "apraxia" of motor sequencing for speech (speech and phonation muscles aren't paralyzed, and function for other activities), producing faltering, dysarthric speech. Lesion in region of Broca's area (Brodmann area 44, see *Figure 5-1*, page 84)
3. **global aphasia**: usually due to lesion that destroys large portion of language center; all aspects of speech and language affected
    A. unable to speak except for some clichés, habitual phrases, or

expletives

B. anomia (inability to name objects or parts of objects)

C. verbal and motor perseveration

D. unable to understand all except for a few words

E. inability to read or write

4. conduction aphasia: due to disruption of connections between frontal and temporal speech areas, usually involving supramarginal gyrus. Similar to Wernicke's (fluent spontaneous speech and paraphasias), but patients understand spoken or written words, and are aware of their deficit. Repetition is severely affected
5. pure word blindness: AKA **alexia without agraphia** (rare) due to lesion in parieto-occipital lobe that interrupts connections between left angular gyrus and both occipital lobes. Patients can write, but are unable to read what they've written, and frequently seem unconcerned about this. Often accompanied by loss of ability to name colors. Reading and naming numbers usually preserved

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5.9.3.2. Brain stem and related syndromes

WEBER'S SYNDROME

Cr. N. III palsy with contralateral hemiparesis (also see *Lacunar strokes*, page 1026). Third nerve palsies from parenchymal lesions may be relatively pupil sparing.

BENEDIKT'S SYNDROME

Similar to Weber's, plus red nucleus lesion. Cr. N. III palsy with contralateral hemiparesis except arm which has hyperkinesia, ataxia, & a coarse intention tremor. Lesion: midbrain tegmentum involving red nucleus, brachium conjunctivum, and fascicles of III.

MILLARD-GUBLER SYNDROME

Facial (VII) & abducens (VI) palsy + contralateral hemiplegia (corticospinal tract) from lesion in base of pons (usually ischemic infarct, occasionally tumor).

PARINAUD'S SYNDROME

AKA dorsal midbrain syndrome, AKA pretectal syndrome. As originally described, a supranuclear paralysis of vertical gaze resulting from damage to the

mesencephalon[50]. There are a number of variations, most include:

1. supranuclear upward gaze palsy (i.e. upgaze palsy affecting both voluntary saccadic and pursuit movements, with preservation of vestibulo-ocular or oculocephalic (doll's eyes) reflexes in most cases). Horizontal eye movements are spared
2. lid retraction (Collier's sign): NB: upgaze palsy + lid retraction produces the "**setting sun sign**"
3. convergence palsy
4. accommodation palsy
5. less common associations: pseudoabducens palsy (AKA thalamic esotropia), seesaw nystagmus, fixed pupils, dissociated light-near response (pseudo-Argyll Robertson), convergence spasm, nystagmus retractorius, internuclear ophthalmoplegia (INO)

Skew deviation may be a unilateral variant.

When combined with downgaze palsy, Parinaud's syndrome **(PS)** is known as the **syndrome of the Sylvian aqueduct**.

Differential diagnosis

Etiologies

1. masses pressing directly on quadrigeminal plate (e.g. pineal region tumors)
2. elevated ICP: secondary to compression of mesencephalic tectum by dilated suprapineal recess, e.g. in hydrocephalus
3. stroke or hemorrhage in upper brainstem
4. multiple sclerosis (MS)
5. occasionally seen with toxoplasmosis

Conditions affecting ocular motility that could mimic the upgaze palsy of PS:

1. Guillain-Barré syndrome
2. myasthenia gravis
3. botulism
4. hypothyroidism
5. there may be a gradual benign loss of upgaze with senescence

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5.9.4. Jugular foramen syndromes

Contents of jugular foramen **(JF)**: Cr. N. IX, X, XI, petrosal sinus, sigmoid sinus, some meningeal branches from the ascending pharyngeal and occipital arteries[51].

Nearby: Cr. N. XII passes through the hypoglossal canal just above the occipital condyle. The carotid artery with the sympathetic plexus enters the carotid canal.

See *Table 5-11* for a summary and *Figure 5-28* for a schematic diagram of deficits in various JF syndromes.

AKA syndrome of the jugular foramen. Damage of nerves in JF itself (IX, X, XI), usually due to intracranial lesion.

Collet-Sicard syndrome: More likely with lesion outside skull. If caused by an intracranial lesion, it would have to be of such a large size that it would usually produce brain stem compression → long tract findings.

Vernet's syndrome: Villaret's syndrome: AKA posterior retropharyngeal syndrome.

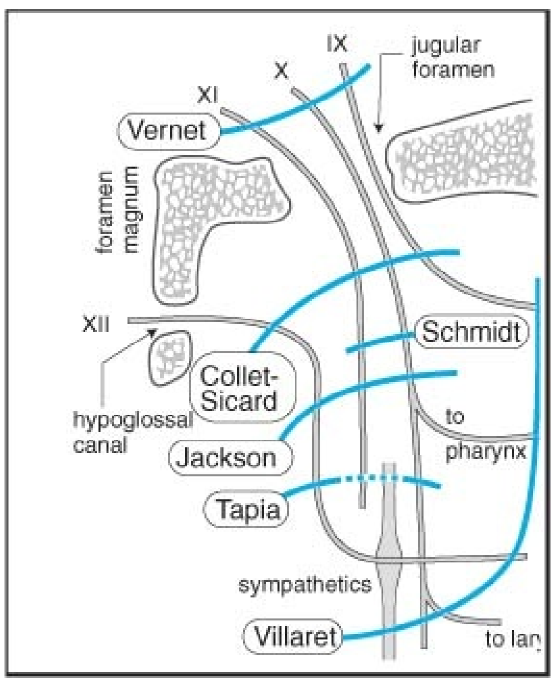

Figure 5-28 Schematic diagram of jugular foramen syndromes (coronal section through left jugular foramen viewed from the front) Solid line through a nerve indicates a deficit, dashed line indicates ± involvement.

Table 5-11 Cranial nerve dysfunction in jugular foramen syndromes

Nerve	Result of lesion	------- SYNDROME* -------					
		Vernet	Collet Sicard	Villaret	Tapia	Jackson	Schmidt
IX	loss of taste and sensation in posterior third of tongue	✖	✖	✖			
X	paralysis of vocal cords & palate, anesthesia of pharynx & larynx	✖	✖	✖	✖	✖	✖
XI	weak trapezius & SCM	✖	✖	✖	±	✖	✖
XII	tongue paralysis & atrophy		✖	✖	✖	✖	
sympathetics	Horner's syndrome			✖	±		

* KEY: ✖ indicates dysfunction of that nerve; ± indicates involvement may or may not occur

5.9.5. Babinski sign

Although regarded as the most famous sign in neurology, there is still disagreement over what constitutes a normal response and when abnormal responses should occur[52]. The following represents one interpretation.

The **plantar reflex (PR)** (AKA Babinski sign) is a primitive reflex, present in infancy, consisting of extension of the great toe in response to a noxious stimulus applied to the foot. The small toes may fan, but this is not consistent nor clinically important. The PR disappears usually at ≈ 10 months age (range: 6 mos to 12 yrs), presumably under inhibitory control as myelination of the CNS occurs, and the normal response then converts to plantarflexion of the great toe. An upper motor neuron **(UMN)** lesion anywhere along the pyramidal (corticospinal) tract from the motor strip down to ≈ L4 will result in a loss of inhibition, and the PR will be "unmasked" producing *extension* of the great toe. With such an UMN lesion, there may also be exaggeration of flexor synergy resulting in dorsiflexion of the ankle, and flexion of the knee and hip (AKA **triple flexor response**).

Neuroanatomy

The afferent limb of the reflex originates in cutaneous receptors restricted to the first sacral dermatome (S1) and travels proximally via the tibial nerve. The spinal cord segments involved in the reflex-arc lie within L4-S2. The efferent limb to the toe extensors travels via the peroneal nerve.

Etiologies

Lesions producing a PR need not be structural, but may be functional and

reversible. etiologies are listed in *Table 5-12*.

Table 5-12 Differential diagnosis of the PR

- spinal cord injuries*
- cervical spinal myelopathy
- lesions in motor strip or internal capsule (CVA, tumor, contusion…)
- subdural or epidural hematoma
- hydranencephaly
- toxic-metabolic coma
- seizures
- trauma
- TIAs
- hemiplegic migraine
- motor neuron disease (ALS)

* in spinal cord injuries, the PR may initially be absent during the period of spinal "shock" (*see page 930*)

Eliciting the PR, and variations

The optimal stimulus consists of stimulation of the lateral plantar surface and transverse arch in a single movement lasting 5-6 seconds[53]. Other means for applying noxious stimuli may also elicit the plantar reflex (even outside the S1 dermatome, although these do not produce toe flexion in normals). Described maneuvers include: **Chaddock** (scratch the lateral foot; positive in 3% where plantar stimulation was negative), **Schaeffer** (pinch the Achilles tendon), **Oppenheim** (slide knuckles down shin), **Gordon** (momentarily squeeze lower gastrocnemius), **Bing** (light pinpricks on dorsolateral foot), **Gonda** or **Stronsky** (pull the 4th or 5th toe down and out and allow it to snap back).

Hoffman's (or Hoffmann's or Hoffmann) sign

May signify a similar UMN interruption to the upper extremities. Elicited by flicking downward on the nail of the middle or ring finger: a positive (pathologic) response consists of involuntary flexion of the adjacent fingers and/or thumb (may be weakly present in normals)[54]. Differs from the plantar reflex since it is monosynaptic (synapse in Rexed lamina IX).

Can sometimes be seen as normal in young individual with diffusely brisk reflexes & positive jaw jerk, usually symmetric. When present pathologically, represents disinhibition of a C8 reflex, ∴ indicates lesion above C8.

Was observed in 68% of patients operated for cervical spondylotic

myelopathy[54]. In 11 patient's presenting with lumbar symptoms but no myelopathy, a bilateral Hoffman sign was associated with occult cervical spinal cord compression in 10 (91%)[54].

5.9.6. Bladder neurophysiology

Central pathways

The primary coordinating center for bladder function resides within the nucleus locus coeruleus of the pons. This center synchronizes bladder contraction with relaxation of the urethral sphincter during voiding[55].

Voluntary cortical control primarily involves inhibition of the pontine reflex, and originates in the anteromedial portion of the frontal lobes and in the genu of the corpus callosum. In an uninhibited bladder (e.g. infancy) the pontine voiding center functions without cortical inhibition and the detrusor muscle contracts when the bladder reaches a critical capacity. Voluntary suppression from the cortex via the pyramidal tract may contract the external sphincter and may also inhibit detrusor contraction. Cortical lesions in this location → urgency incontinence with inability to suppress the micturition reflex[43 (p 1031)].

Efferents to the bladder travel in the dorsal portion of the lateral columns of the spinal cord (blue areas in *Figure 5-29*).

Motor

There are two sphincters that prevent the flow of urine from the bladder: internal (autonomic, involuntary control), and external (striated muscle, voluntary control).

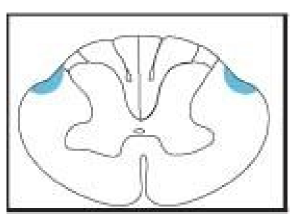

Figure 5-29 Location of spinal cord bladder efferents (blue)

Parasympathetics (PSN): the detrusor muscle of the bladder contracts and the internal sphincter relaxes under PSN stimulation. PSN preganglionic cell bodies reside in the intermediolateral grey of spinal cord segments S2-4. Fibers exit as ventral nerve roots and travel via pelvic splanchnic nerves (nervi

erigentes) to terminate on ganglia within the wall of the detrusor muscle.

Somatic nerves: somatic voluntary control descends in the pyramidal tract to synapse on motor nerves in S2-4, and then travels via the **pudendal nerve** to the external sphincter. This sphincter may be voluntarily contracted, but relaxes reflexly with opening of the internal sphincter at the initiation of micturition. Primarily maintains continence during ↑ vesical pressure (e.g. valsalva).

Sympathetics: sympathetic cell bodies lie within the intermediolateral gray column of lumbar spinal cord from segments T12 - L2. Preganglionic axons pass through the sympathetic chain (without synapsing) to the inferior mesenteric ganglion. Postganglionic fibers pass through the inferior hypogastric plexus to the bladder wall and internal sphincter. Sympathetics heavily innervate the bladder neck and trigone. Sympathetics have little effect on bladder motor activity, but alpha adrenergic stimulation results in bladder neck closure which is necessary for bladder filling.

Pelvic nerve stimulation → increased sympathetic tone → detrusor relaxation & increased bladder neck tone (allowing larger volume to be accommodated).

SENSORY

Less well understood than motor innervation. Bladder wall stretch receptors sense bladder filling and send afferent signals via pelvic, pudendal and hypogastric nerves to spinal cord segments T10-L2 & S2-4. Fibers ascend primarily in the spinothalamic tract.

URINARY BLADDER DYSFUNCTION

The term **neurogenic bladder** describes bladder dysfunction due to lesions within the central or peripheral nervous systems. Some use the term synonymously with detrusor areflexia.

Dorsal (sensory) roots lesions interrupt the afferent limb, producing an atonic bladder that fills until dribbling and overflow incontinence occur. No sensation of bladder fullness is appreciated. Voluntary voiding is still possible, but is usually incomplete.

Detrusor hyperreflexia: Can result from interruption of efferents anywhere from cortex to sacral cord. When a critical volume is attained, reflex bladder emptying occurs. Clinically associated with frequent, uncontrollable, precipitous voiding. Cerebral lesions include: CVA, head injury, brain tumors, hydrocephalus, Parkinson's disease, various dementias, and MS. Cord lesions include anything that causes myelopathy (see *Myelopathy*, page 1185).

Detrusor areflexia: Clinically correlates with difficulty initiating micturition, interrupted flow, and significant residual urine. Incontinence may result from over-distention of the bladder (**overflow incontinence**), or may be associated with absence of sphincter tone. Etiologies include: chronic infection, long-term bladder catheterization, certain drugs (especially phenothiazines), injury or tumor of the cauda equina or conus medullaris, myelomeningocele, and diabetes mellitus (autonomic neuropathy).

In general, regarding discrete neurologic lesions affecting the bladder[56]:

1. **supraspinal** (lesions above the brain stem): loss of centrally mediated inhibition of the pontine voiding reflex. Usually produces involuntary bladder contractions with smooth and striated sphincter synergy, often with preserved sensation and voluntary striated sphincter function. Symptoms: urinary frequency or urgency, urgency incontinence, and nocturia[55]. If sensory pathways are interrupted, unconscious incontinence occurs (incontinence of the unawares type). Since muscles are coordinated, normal bladder pressures are maintained and there is low risk of high-pressure related renal dysfunction. Voluntary bladder emptying is usually maintained, and timed voiding together with anticholinergic medications are used in management. Areflexia may sometimes occur
2. complete (or near complete) **spinal cord lesions**:
   A. **suprasacral** (lesion above the S2 spinal cord level, which is ≈ T12/L1 vertebral body level in an adult): the sacral voiding center is located in the conus medullaris. Etiologies: spinal cord injuries (after spinal shock has subsided[A]), tumors, transverse myelitis. Usually develop detrusor hyperreflexia → involuntary bladder contractions without sensation (**automatic bladder**), smooth sphincter synergy, but striated dyssynergy (involuntary contraction of the external sphincter during voiding which produces a functional outlet obstruction with poor emptying and high vesical pressures). Bladder fills and empties spontaneously (or in response to lower extremity cutaneous stimulation). Bladder compliance is often reduced. Managed by intermittent catheterizations + anticholinergics
   B. **infrasacral lesions** (lesion below the S2 spinal cord level): includes injury to conus medullaris, cauda equina or peripheral nerves (formerly referred to as lower motor neuron lesions). Etiologies: large HLD, trauma with compromise of spinal canal. Usually develop detrusor areflexia, and do not have involuntary bladder contractions. Reduced urinary flow rate or retention results, and voluntary voiding

may be lost. Overflow incontinence develops. There may be reduced compliance during filling, and paralysis of the smooth sphincter. Usually associated with loss of bulbocavernosus and anal wink reflex (preserved in suprasacral lesions) and perineal sensory loss

3. **interruption of the peripheral reflex arc**: may produce disturbances similar to low spinal cord injury with detrusor areflexia, low compliance and inability to relax the striated sphincter
4. herniated lumbar disc: (*see page 443*) most consist initially of difficulty voiding, straining, or urinary retention. Later, irritative symptoms may develop
5. spinal stenosis (lumbar or cervical): urologic symptoms vary, and depend on the spinal level(s) involved and the type of involvement
6. cauda equina syndrome: usually produces urinary retention, although sometimes incontinence may occur (some cases are overflow incontinence) (*see page 446*)
7. peripheral neuropathies: e.g. with diabetes, usually → impaired detrusor activity
8. neurospinal dysraphism: most myelodysplastic patients have an areflexic bladder with an open bladder neck. The bladder usually fills until the resting residual fixed external sphincter pressure is exceeded and the leakage occurs
9. **multiple sclerosis**: 50-90% of patients develop voiding symptoms at some time. The demyelination primarily involves the posterior and lateral columns of the cervical spinal cord. Detrusor hyperreflexia is the most common urodynamic abnormality (in 50-99% of cases), with bladder areflexia being less common (5-20%)

A. during spinal shock (*see page 930*), the bladder is acontractile and areflexic (detrusor areflexia); sphincter tone usually persists and urinary retention is the rule (urinary incontinence generally does not occur except with overdistention)

URINARY RETENTION

Etiologies of urinary retention:

1. bladder outlet obstruction (a brief differential diagnosis list is presented here)
    A. urethral stricture: retention tends to be progressive over time

B. prostatic enlargement in males:
   1. benign prostatic hypertrophy **(BPH)** & prostate cancer: retention tends to be progressive over time
   2. acute prostatitis: onset of retention may be <u>sudden</u>
   3. rare: extruded prostatic stone

C. women may develop a cystocele which can produce a urethral kink

D. rare: urethral cancer

2. detrusor areflexia (*see page 117*) or hypotonia
   A. spinal cord injury
   B. cauda equina syndrome (*see page 446*)
   C. chronic infectinon
   D. long-term bladder catheterization
   E. certain drugs (narcotics, phenothiazines)
   F. injury of the cauda equina or conus medullaris, or of the spinal cord at or below the sacrum
      1. trauma
      2. tumor
      3. myelomeningocele
   G. diabetes mellitus (autonomic neuropathy)
   H. herpes zoster at the level of the sacral dorsal root ganglia[56] (p 967)
   I. incomplete opening of the bladder neck: occurs almost exclusively in young males with longstanding obstructive and irritative symptoms[56] (p 968)
   J. following severe bladder over distention from any of the above
3. postoperative retention: well-recognized but poorly understood. More common after lower urinary tract, perineal, gynecologic and anorectal operations. Anesthesia and analgesia may contribute to a number of factors[56] (p 969)
4. psychogenic

EVALUATION OF BLADDER FUNCTION

URODYNAMICS

Usually combined with x-ray (cystometrogram **(CMG)**) or fluoro (videourodynamics). Measures intravesicular pressures during retrograde bladder filling through a urethral catheter, usually combined with sphincter electromyography. Presence or absence (detrusor areflexia, *see below*) of

detrusor reflex is detected. If present, procedure is repeated, asking patient to suppress the urge to void. Inability to suppress is called an un-inhibited detrusor reflex (AKA detrusor hyperreflexia, *see above*).

SPHINCTER ELECTROMYOGRAPHY ***(EMG)***

Either via needle electrodes, or with externally mounted surface electrodes. Voluntary sphincter contraction tests intactness of supraspinal innervation. When combined with CMG, detects electrical activity in sphincters during associated phases of detrusor contraction.

VOIDING CYSTOURETHROGRAM AND INTRAVENOUS PYELOGRAPHY ***(IVP)***

Voiding cystourethrogram **(VCUG)** detects urethral pathology (diverticula, strictures…), abnormalities of bladder (diverticula, detrusor trabeculations associated with longstanding contractions against high resistance…), and vesical-ureteral reflux.

TREATMENT

Goals are to preserve renal function (which usually involves prevention of UTIs, renal calculi, and ureteral reflux due to high intravesicular pressures) and optimization of urinary continence. Patients with inadequate emptying or increased bladder pressure are often managed by intermittent catheterizations and anticholinergics. Anticholinergics and behavioral therapy are used for patients with maintained voluntary bladder emptying with urinary frequency or urgency incontinence.

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NOTES

6. Neuroradiology

6.1. Contrast agents in neuroradiology

Also see *Intraoperative dyes*, page 144 for visible dyes useful in the operating room.

IODINATED CONTRAST AGENTS

✖ Caution: iodinated contrast (IV or intraarterial) may delay excretion of **metformin** (Glucophage®, Avandamet®), an oral hypoglycemic agent used in diabetes type II, and can be associated with lactic acidosis and renal failure. The manufacturer recommends withholding metformin 48 hrs prior to and following contrast administration (or longer if there is evidence of declining renal function following use of contrast). Metformin should also be held ≈ 48 hours before any surgery, and should not be restarted post-op until the patient has fully recovered and is eating and drinking normally.

Maximum dose of iodine with normal renal function is ≈ 86 gm in a 24 hour period.

INTRATHECAL CONTRAST AGENTS

The primary approved agent employed for intrathecal use today is iohexol (Omnipaque®) (*see below*).

Inadvertent intrathecal injection of ionic contrast agents

✖ Caution: serious reactions can occur with inadvertent intrathecal injection (e.g. for myelography, cisternography, ventriculography…) of iodinated contrast media that are not specifically indicated for intrathecal use (including ionic contrast agents as well as some non-ionic agents (e.g. Optiray®, Reno-60…)). This can cause uncontrollable seizures, intracerebral hemorrhage, cerebral edema, coma, paralysis, arachnoiditis, myoclonus (tonic-clonic muscle spasms), rhabdomyolysis with subsequent renal failure, hyperthermia, and respiratory

compromise, with a significant fatality rate[1].

Management suggestions include:

1. immediately remove CSF + contrast if the error is recognized when the opportunity is available (e.g. withdraw fluid through myelography needle)
2. elevate head of bed ≈ 45° (to keep contrast out of head)
3. if there is a question about what may have occurred (i.e. it is not certain if an inappropriate contrast agent was used) send blood and CSF with contrast for high-performance liquid chromatography for identification of agent[2]
4. antihistamines: e.g. diphenhydramine (Benadryl®) 50 mg deep IM
5. respiration: supplemental oxygen, and if needed, intubation
6. control HTN
7. IV hydration
8. IV steroids
9. sedation if patient is agitated
10. treat fever with acetaminophen and if needed with a cooling blanket
11. pharmacologic paralysis if necessary to manage muscle activity
12. anticonvulsant medication: more than one agent may be required (e.g. phenytoin + phenobarbital + a benzodiazepine)
13. consider unenhanced brain CT scan: may help assess if contrast has diffused intracranially, but this requires placing patient flat and may not be advisable
14. insertion of lumbar subarachnoid drain
15. monitor: electrolytes, anticonvulsant levels, creatine kinase **(CK)**
16. repeat EEGs to assess seizure activity while sedated/paralyzed

Iohexol (Omnipaque®)

A non-ionic triiodinated compound. It has replaced metrizamide. Concentrations expressed as follows: e.g. Omnipaque 300 contains the equivalent of 300 mg of organic iodine per ml of media (300 mgI/ml).

Usually reserved for IV contrast CT scan of brain primarily for patients with previous dye reaction, e.g. to Reno-60. Uses and concentrations are shown in *Table 6-1*.

Table 6-1 Iohexol concentrations for adults

Procedure	Concentration (mgI/ml)	Volume (ml)
lumbar myelography via LP	180 240	10-17 7-12.5
thoracic myelography via LP or cervical injection	240 300	6-12.5 6-10
cervical myelography via LP	240 300	6-12.5 6-10
cervical myelography via C1-2 puncture	180 240 300	7-10 6-12.5 4-10
complete myelography via LP	240 300	6-12.5 6-10
cerebral arteriography*	300	≈ 6-12 ml/vessel
IV contrast enhanced CT scan of the brain	240 350	120-250 ml IV drip 70-150 ml bolus†
CT cisternography via LP or C1-2 puncture	300 350	12 12
CT ventriculography via ventricular catheter	180‡	2-3
plain film ventriculography via ventricular catheter	180	2-3
plain film "shunt-o-gram" injected via shunt into ventricles	180	2-3
plain film "shunt-o-gram" injected via shunt <u>distal</u> to valve so as not to enter into ventricles (to check distal shunt function)	300 350	10-12 10-12

* most centers use Optiray®, see text

† follow with 250 ml bolus of 0.45% NS to rehydrate patient

‡ 180 will be very dense on CT, and some use 1-3 ml of 140 or diluted 180%(dilute approximately 2 parts contrast to 1 part preservative-free normal saline)

Intrathecal use: NB: only Omnipaque 180, 210, 240 and 300 are labeled for intrathecal use. 140 and 350 are <u>not</u> FDA approved for intrathecal use, however, some neuroradiologists will use Omnipaque 140 or diluted 180 e.g. for CT ventriculography.

Consider discontinuing neuroleptic drugs (including: phenothiazines, e.g. chlorpromazine, prochlorperazine, and promethazine) at least 48 hours prior to procedure. Elevate HOB ≥ 30° for the first few hours after the procedure. Hydrate orally or IV.

Use with caution in patients with seizure history, severe cardiovascular

disease, chronic alcoholism or multiple sclerosis.

Iohexol undergoes slow diffusion from the intrathecal space to the systemic circulation and is eliminated by renal excretion with no significant metabolism or deiodination.

Maximum dosage: a total dose of 3060 mg iodine should not be exceeded in an adult during a single myelogram (some say up to 4500 mg is OK) (e.g. 15 cc of Omnipaque 300 = 15 ml **x** 300 mgI/ml= 4500 mg of iodine).

Iopamidol (e.g. Isovue 300, Isovue 370®)

Triiodinated, non-ionic, water-soluble. Used for intravascular and intrathecal radiographic contrast. Isovue 300 and 370 contains 300 and 270 mg iodine/ml, respectively.

NON-INTRATHECAL CONTRAST AGENTS

For inadvertent intrathecal injection of contrast agents <u>not</u> intended for intrathecal use, *see above*.

Diatrizoate meglumine (e.g. Reno-60®, Reno-dip®)

✖ Not for intrathecal use (*see above*).

A tri-iodinated benzine derivative similar to Conray. Both have been available for a long time. Due to the fact that it ionizes, it is <u>ionic</u> and <u>hyperosmolar</u>. Widely used IV, in neuroradiology for IV contrast enhanced CT **(CECT)** scan when there is no history of prior reaction to IV contrast agents (use iohexol in patients with previous reaction, *see above*).

- CECT of the brain in adult patient with no history of previous dye reaction:
  - A. 300 ml IV drip of Reno-dip® (30% solution, i.e. 300 mg/ml) over ≈ 15 mins
  - B. 50-150 ml of Reno-60 (60% solution). Typically: 150 ml is used
- body CT: bolus of 150 ml of Reno-60® (3 vials of 50 ml each), followed e.g. by 250 ml of 0.45% NS to help prevent dehydration. Usually given more slowly to diabetics and the elderly where there is increased risk of renal failure

Ioversol (Optiray®)

✖ Not for intrathecal use (*see above*).

Uses and concentrations include:

- arteriography: Optiray 300 (ioversol 64%) or Optiray 320 (ioversol 68%). Total procedural dose should not usually exceed 200 ml
- IV contrast enhanced CT scan of brain:
  A. adult: 50-150 ml of Optiray 300, 320, or 100-250 ml of Optiray 240. Typically: 100 ml of Optiray 320
  B. pediatrics: 1-3 ml/kg of Optiray 320

Iopromide (Ultravist®)

✖ Not for intrathecal use (*see above*). Available in 150, 240, 300 & 370 mg iodine/ml. Osmolality of Ultravist 300 is 607.

Cerebral angiography (300 mg/ml): maximum dose is 150 ml per procedure.

Contrast enhanced CT **(CECT)** (**300 mg/ml**). ***Rx*** Pediatrics (> 2 years age): typical dose in is 1-2 ml/kg IV, maximum dose is 3ml/kg per procedure. Adult: typical dose is 50-200 ml, maximum dose is 200 ml.

Iodixanol (Visipaque®)

✖ Not for intrathecal use (*see above*). Triiodinated, non-ionic, iso-osmolar to blood. For intravascular use. FDA approved for CECT, some angiographers use Visipaque 270 for cerebral angiography (slightly lower opacification, but also slightly lower iodine dose). Available in 270 and 320 mg iodine/ml.

6.1.1. Iodinated contrast preps

6.1.1.1. Allergy prep

Indicated for patients with previous history of reaction to IV iodinated contrast material. Minor previous reactions such as hives and itching should merit preparation with this regimen whenever possible. Patients with anaphylactic shock or severe edema causing compromise of the airway should probably not receive IV iodine even with this prep, unless absolutely necessary. ✖ Caution: the patient may still have serious reaction (modified[3]). This prep has also been used for the rare gadolinium allergy.

1. utilize non-ionic contrast medium (e.g. iohexol) whenever possible
2. have emergency equipment available during study
3. medications:
   A. steroid (*see page 31* for further details of steroid dosing)

1. prednisone 50 mg PO: 20-24 hrs, 8-12 hrs & 2 hrs before study
2. equivalent dose of IV Solumedrol® (methylprednisolone): ≈ 25 mg

B. diphenhydramine (Benadryl®) 50 mg, *EITHER* IM 1 hr before, *OR* IV 5 min before study

C. optional: H_2 antagonist, e.g. cimetidine 300 mg PO or IV 1 hr before study

Medications for an emergency scan when 24 hour prep is not possible:

- hydrocortisone 100 mg IV then scan within 2 hours

6.1.1.2. Prep for renal insufficiency

For patients with DM or mild renal insufficiency (e.g. slight serum creatinine elevation, > 1.2 mg/dL (U.S.) which is > 100 µmol/L), to mitigate against iodine contrast-induced nephropathy:

- N-acetyl cysteine (Mucomyst)[A]: regimens all accompany hydration and include:
  A. 800 mg PO q 8 hrs for 24 hours before the study[4], followed by 600 mg PO BID for 24 hours after the study
  B. 600 mg PO BID X 2 days before the study, 600 mg PO BID for 24 hours after
  C. 600-mg IV bolus before the study, and 600 mg PO BID for 48 hours after[5]
- hydration: 1 L of sterile water with 3 amps of sodium bicarbonate IV at 100 ml/hr, start 1 hour prior to the study, and continue until entire L given

A. the actual efficacy of NAC has not been proven, and may be no better than hydration alone

6.1.2. Reactions to intravascular contrast media

BETA BLOCKERS

Beta blockers can increase the risk of contrast media reactions, and may mask some manifestations of an anaphylactoid reaction.

They also make use of epinephrine inadvisable since the alpha effects of epinephrine will predominate (bronchospasm, vasoconstriction, increased vagal

tone). If treatment is required for hypotension, may try **glucagon** 2-3 mg IV bolus, followed by 5 mg IV drip over 1 hour (glucagon has positive inotropic and chronotropic effect that is not mediated through adrenergic pathways).

IDIOSYNCRATIC REACTIONS AND TREATMENT

For treatment of inadvertent intrathecal injection of ionic contrast agents, *see page 122*.

HYPOTENSION WITH TACHYCARDIA (ANAPHYLACTOID REACTION)

1. mild: Trendelenburg position. IV fluids
2. if no response but remains mild:
   epinephrine (use with caution in patients with coronary artery disease, limited cardiac reserve, hypertension, or unclipped cerebral aneurysm)
   A. 0.3-0.5 ml of 1:1000 SQ (0.3-0.5 mg) q 15-20 mins (peds: 0.01 mg/kg)
   B. or, ASEP recommendations (especially for elderly or patients in shock): 10 ml of 1:100,000 IV over 5 to 10 min (put 0.1 ml of 1:1000 in 10 ml of NS, or dilute 1 amp of 1:10,000 to 10 ml with NS)
3. moderate to severe or worsening (anaphylaxis): add:
   A. IV colloidal fluids, e.g. hetastarch (Hespan®) 6% (colloids are required since there is extravascular shift of fluids due to seepage, these agents also carry a small risk of allergic reaction)
   B. epinephrine (*see above*). May repeat **x** 1
   C. O_2 2-6 L/min per NC. Intubate if necessary
   D. EKG to R/O ischemic changes
4. if shock develops: add dopamine, start at 5 mcg/kg/min (*see page 22*)

HYPOTENSION WITH BRADYCARDIA (VASOVAGAL REACTION)

1. mild:
   A. Trendelenburg position
   B. IV fluids
2. if no response, add:
   A. atropine 0.75 mg IV, may repeat up to 2-3 mg over 15 mins PRN. Use with caution in patients with underlying heart disease
   B. EKG and/or cardiac monitor: especially if atropine or dopamine are used
3. if no response: add dopamine, start at 5 mcg/kg/min (*see page 22*)

Urticaria

1. mild: self limited. No treatment necessary
2. moderate:
   A. **diphenhydramine** (Benadryl®) 50 mg PO or deep IM (avoid IV, can cause anaphylaxis itself)
   B. **cimetidine** (Tagamet®) 300 mg PO or IV diluted to 20 ml and given over 20 mins. H_2 receptors contribute to wheal and flare of reaction
3. severe: treat as above for moderate reaction, and add:
   A. epinephrine (*see above*)
   B. maintain IV line

Facial or laryngeal angioedema

1. epinephrine: *see above*. May repeat up to 1 mg
2. if respiratory distress: O_2 2-6 L/min. Intubate if necessary (orotracheal may be very difficult due to swelling of tongue, nasotracheal intubation or emergency cricothyrotomy may be required)
3. diphenhydramine: *see above*
4. cimetidine: *see above*
5. if angioedema is accessible, add ice pack
6. maintain IV line
7. steroids are usually effective only for <u>chronic</u> angioedema

Bronchospasm

1. mild to moderate:
   A. epinephrine: *see above*. May repeat up to 1 ml
   B. if respiratory distress: O_2 2-6 L/min. Intubate if necessary
   C. maintain IV line
   D. inhalational therapy with a ß-adrenergic agonist, e.g. albuterol (Proven-til®) if respiratory therapy is available, otherwise, metered dose inhaler e.g. pirbuterol (Maxair®) or metaproterenol (Metaprel®), 2 puffs
2. severe: treat as above for moderate reaction, and add:
   A. aminophylline 250-500 mg in 10-20 cc NS slow IV over 15-30 mins. Monitor for hypotension and arrhythmias
   B. intubate
3. prolonged: add the following (will not have immediate effect):

   A. hydrocortisone 250 mg IV
   B. diphenhydramine: *see above*
   C. cimetidine: *see above*

PULMONARY EDEMA

1. O_2 2-6 L/min per NC. Intubate if necessary
2. raise head and body
3. furosemide (Lasix®) 40 mg IV
4. EKG
5. if hypoxia develops (may manifest as agitation or combativeness), add:
   A. morphine 8-15 mg IV. May cause respiratory depression, be prepared to intubate
   B. epinephrine: *see above*. ✖ CAUTION: use only if MI can be R/O as cause of the pulmonary edema. Patients with acute intracranial pathology may be at risk of neurogenic pulmonary edema (*see page 28*)

SEIZURES

If seizure is not self limited, start with lorazepam (Ativan®) 2-4 mg IV for an adult. Take precautions for status epilepticus (*see page 404*) and proceed to other drugs as indicated (*see page 405*).

6.2. Radiation safety for neurosurgeons

Radiation exposure has both a deterministic component (exposure over a certain threshold will cause a specific injury) as well as a stochastic component (any dose increases the chances of an adverse event, and the higher the cumulative dose, the higher the chances).

UNITS[6]

Absorbed dose: the amount of energy absorbed per unit mass. Expressed in Gray or rads.

Gray (Gy): the SI unit. 1 Gy = 100 cGy = 100 rads = an absorbed dose of 1 Joule/kg.

Rad: 1 rad = an absorbed dose of 100 ergs/gram = 0.01 joule/kg = 0.01 Gy =

1 cGy.

The biological effect (dose equivalent) of radiation: can be expressed in rem or Sieverts.

Sievert (Sv): the SI unit. The dose equivalent in sieverts is equal to the absorbed dose in grays multiplied by a "quality factor" **(Q)** which differs for different sources of radiation, e.g. high-energy protons have a Q of 10, x-rays have a Q of 1. 1 Sv=100 rems.

Roentgen-equivalent man (rem): the absorbed dose in rads multiplied by Q. 1 rem is estimated to cause ≈ 300 additional cases of cancer per million persons (one third of which are fatal). 1 rem = 0.01 sievert.

TYPICAL RADIATION EXPOSURE

The average annual exposure to radiation is 360 mrem (about 30 mrem are due to background cosmic radiation). A transcontinental airline flight exposure is ≈ 5 mrem.

CXR: causes about 0.01-0.04 rem of exposure to the chest.

Spine x-ray with obliques: 5 rem.

CAT scan (brain, noncontrast): median effective dose to the head = 0.2 rem, but the range varied 13 fold within and across institutions[7].

Spine CT: 5 rem.

Cerebral arteriogram: ≈ 10-20 rem (including fluoroscopy)[9].

Cerebral embolization: 34 rem.

Bone scan: 4 rem.

C-arm fluoroscopy[8]: exposure is shown in *Table 6-2*.

Doses during a minimally invasive TLIF[10]:

Patient exposure: mean 60 mGy to the skin in the AP plane (range: 8-250 mGy), 79 mGy in the lateral plane.

Surgeon exposure: 76 mrem to dominant hand, 27 mrem at the waist under a lead apron, and 32 mrem to an unprotected thyroid level detector.

Table 6-2 Radiation exposure with fluoroscopy[8]*

Distance from beam		Typical team member	Deep exposure	Superficial exposure
feet	meters		(mrem/min)	
Direct beam		patient	4000	
1	0.3	surgeon	20	29
2	0.6	assistant	6	10
3	0.9	scrub tech	0	≤ 2
5	1.5	anesthesiologist	0†	0†

* in a mock OR set up for maximal scatter

† after 10 minutes of exposure

Occupational exposure

The U.S. Nuclear Regulatory Commission **(NRC)** maximal recommended annual occupational dose limits for radiation are shown in *Table 6-3*.[11]. The 1990 recommendations of the International Commission on Radiological Protection **(ICRP)** was to keep exposure ≤ 2 rem/year averaged over 5 years[12].

ALARA: an acronym for "As Low As Reasonably Achievable" by which the NRC means making every reasonable effort to keep radiation dose as far below the limits as possible consistent with the purpose for which the licensed activity is undertaken[13].

Table 6-3 Annual occupational radiation dose limits

Target organ	Recommended MAXIMAL dose (rem/yr)
whole body	**5**
lens of eye	15
skin, hands, feet	50
other organs (including thyroid)	15

Steps to reduce occupational radiation dose (to staff) during surgery:

1. increase the distance from the radiation source: radiation exposure is proportional to the inverse square of the distance. Conventional wisdom is to try to keep 6 feet away. In a AANS publication, **3 m** (10 ft) was recommended[14]

   Lead aprons/shields may or may not work. Distance ALWAYS works[19] (inverse square law - double the distance and get 1/4 the radiation!).

2. use shielding: shielding is less effective at higher kV (used with larger patients). Portable lead "doors" are more effective than aprons. Wrap-around 2-piece aprons are better than front side aprons. Non-lead aprons may not provide the rated protection at levels > 100 keV[15]
3. don't overuse magnification: most fluoro systems increase the radiation emitted **x** ≈ 4 to compensate for the associated reduction in image brightness
4. "boost" mode can double the radiation output. Use should be kept to a minimum
5. use live fluoro only when absolutely necessary
6. for lateral imaging, stand on the "downstream" (image intensifier **(ImI)**) side of the C-arm: scatter is the most significant cause of exposure here and is higher on the source side[16] (this asymmetry is not as significant for C-spine[17])
7. keep the ImI as close to the patient as possible (reduces patient & staff exposure)
8. on AP images (with the patient prone or supine): position the x-ray tube under the table with the ImI over the patient (lowers scatter exposure to staff)[18]
9. collimate the beam as much as possible: reduces radiation to patient and to staff, and results in less image degradation
10. keep hands, arms, etc. out of the primary beam at all times (consider using leaded gloves if hands need to be within the beam or nearby for an extended time)
11. minimize number of images: plan your shot, avoid frequent "checks" or peeks
12. use image guided navigation when possible and practical
13. leaded glasses are recommended only for personnel with very high fluoro times: cataracts can be induced by single doses of 200 rads (very high), cumulative doses of 750 rads have not been associated with cataracts

6.3. CAT scan or CT scan

Attenuation of the x-ray beam on a CT scan is defined in Hounsfield units. These units are not absolute, and vary between CT scanner models. Some sample values are shown in *Table 6-4*.

If there are no calibration marks on a scan, one can estimate the average adult globe (eyeball) is 25 mm in diameter (through its equator).

Table 6-4 Hounsfield units for a sample CT scanner

DEFINITIONS	Hounsfield units	Comment
no attenuation (air)	–1000	definition
water	0	definition
dense bone	+1000	definition
CRANIAL CT		
brain (grey matter)	30 to 40	
brain (white matter)	20 to 35	
cerebral edema	10 to 14	
CSF	+5	
bone	+600	
blood clot*	75 to 80	acute SDH or EDH, fresh SAH
fat	–35 to –40	
calcium	100 to 300	
enhanced vessels	90-100	
SPINE CT		
disc material	55-70	disc density is ≈ 2 **x** thecal sac
thecal sac	20-30	

* Hct < 23% will cause an acute SDH to be isodense with brain

Differential diagnosis of an intracranial hyperdense (with respect to brain) structure on non-contrast CT:

1. acute blood
2. calcium
3. vessels with low flow
4. melanoma: may be slightly hyperdense to brain due to melanin

Contrast enhanced CT scan (CECT)

Used primarily for imaging neoplasms or vascular malformations.

Typical IV dose of contrast: 60-65 ml of e.g. Isovue 300® (*see page 123*) which delivers 18-19.5 grams of iodine.

6.3.1. CT angiography (CTA)

Employs rapid injection of iodinated contrast at 3-4 cc/sec, typically 65-75 ml of e.g. Isovue 300®.

Accuracy is diminished for vessels that are perpendicular to the axial CT plane. Also in the vicinity of dense clot, CTA has trouble resolving the adjacent vessels.

6.3.2. CT perfusion (CTP)

Requires use of iodinated contrast. Areas of interest are selected from an unenhanced CT scan in the 3 supratentorial vascular territories. Contrast is given at a standard rate (e.g. 40 ml IV at 5 ml/sec). Scans through the regions of interest are repeated at intervals, e.g. every 2 seconds for 1 minute.

Acetazolamide (ACZ) (Diamox®) **challenge**: after the above, a bolus of 1000 mg of IV ACZ is given, and scans are repeated at intervals for approximately 10 minutes, with a final scan usually at 15 minutes. Parameters then calculated from the images: cerebral blood volume **(CBV)**, CBF, meant transit times **(MTT)**, and time to peak **(TTP)**.

Abnormalities that can be demonstrated (also, *see page 1011*):

1. flow significant stenosis: decreased CBV & CBF, increased MTT and TTP
2. steal: after ACZ challenge (*see above*), CBV & CBF decrease, often with increases in the corresponding contralateral territory; MTT increases

In comparison to perfusion weighted MRI **(PWI)** (*see page 132*):

1. PWI acquires multiple slices of the whole brain over and over. CTP is limited to a given slice or several slices (usually 10-20 mm thick), and one has to choose where to place that slice
2. PWI has more artifact than CTP

6.4. Magnetic resonance imaging (MRI)

6.4.1. General information

DEFINITIONS[20]

Abbreviations

TR	time to repetition
TE	time to echo
T_I	time to inversion
T_1	spin-lattice relaxation time ("time to magnetize") (regrowth)
T_2	spin-spin relaxation time ("time to demagnetize") (decay)

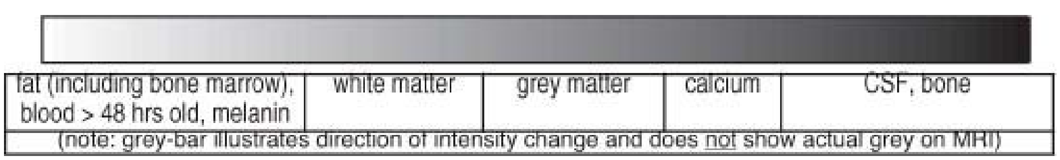
Table 6-5 Range of acquisition data

	short TE (te < 50)	long TE (te > 80)
short TR (TR < 1000)	T1WI	
long TR (TR > 2000)	proton density or spin density	T2WI

T_1 weighted image (T1WI)

Short T_1 → high signal (bright). "Anatomic image", somewhat resembles CT. Shorter acquisition time than T2WI. Proton rich tissue (e.g. H_2O) has long T_1.

Clues to recognizing T1WI: CSF is black, subcutaneous fat is white, TR and TE are short (hundreds and double digits, respectively).



★ The only objects that appear white on T1WI are: fat, melanin, Onyx® (*see page 1102*), and subacute blood (> 48 hrs old). White matter is higher signal than grey matter (myelin has a high fat content). Most pathology is low signal on T1WI.

T_2 weighted image (T2WI)

Long T_2 → high signal (bright). "Pathological image". Most pathology shows up as high signal, including surrounding edema.

Clues to recognizing T2WI: CSF is white, TR & TE are long (thousands and

hundreds, respectively).

Differentiating blood and fat: both fat and 7-14 day-old blood (see *Table 32-4*, page 1125) are high signal on T1WI. On T2WI blood remains high signal but fat "drops out" and becomes black.

Spin density image

AKA balanced image, AKA proton density image. Partway between T1WI and T2WI. CSF = grey, approximately isodense with brain (useful in white matter demyelinating disease).

FLAIR

Acronym: FLuid-Attenuated Inversion Recovery. Long TR and TE. Resembles a T2WI except the CSF is nulled out (appears dark). The grey/white intensity pattern is reversed from T1WI and is more prominent. Most abnormalities including MS plaques, other white matter lesions, tumors, edema, encephalomalacia, gliosis and acute infarcts appear bright. Periventricular lesions such as MS plaques become more conspicuous. Also good for demonstrating abnormalities in CSF.

Differential diagnosis of increased signal in subarachnoid spaces on FLAIR:

1. subarachnoid hemorrhage (SAH): ★ the best sequence for detecting SAH on MRI
2. meningitis: occurs in some cases
3. meningeal carcinomatosis
4. superior sagittal sinus thrombosis
5. stroke
6. adjacent tumor: ? if related to higher protein
7. previous administration of gadolinium
8. high levels of FIO_2 especially at levels nearing 100% as may be used in patients getting MRI under general anesthesia[21]. Shows up in basal cisterns and in sulci over the convexity, but not in ventricles

Echo train (AKA fast spin echo (FSE))

tr is held constant, te is progressively increased utilizing multiple echoes (8-16) rather than 1. Image approaches T2WI but with substantially reduced acquisition time (fat is brighter on FSE, which may be rectified by fat suppression techniques).

Gradient echo

AKA T2* (called T2-star), and some manufacturers have trademarked names for this, e.g. "GRASS" (a GE trademarked acronym for Gradient Recalled Acquisition in a Steady State) or FISP. A "fast" T2WI utilizing a partial flip angle. CSF and flowing vessels appear white. Bone, calcium and heavy metals are dark. Typical acquisition data: TR = 22, TE = 11, angle 8°. Used e.g. in cervical spine to produce a "myelographic" image, improves MRI's ability to delineate bony spurs. Also shows small old cerebral hemorrhages (seen in 60% of patients presenting with hemorrhagic infarction, and in 18% with ischemic infarcts[22]); these patients may be at increased risk of hemorrhage from anticoagulation. ★ Gradient-echo T2WI MRI is the most sensitive test for blood (which appears dark) due to high sensitivity to paramagnetic artifact.

"STIR" image

Acronym for "Short Tau Inversion Recovery". Summates T_1 & T_2 signals. Causes fat to drop out - sometimes also called **fat suppression** or "**fat sat**" (for fat saturation), allows gadolinium enhancement to show up better in areas of fat. Useful primarily in spine and orbit. Very good for showing bone edema (can help in dating spine fractures). The dorsal root ganglion may enhance on fat suppression images.

MRI contrast

Current agents are mostly based on gadolinium (a rare earth metal which is para-magnetic in solutions) include: gadopentatate dimeglumine (Magnevist®), gadodiamide (Omniscan®), gadoversetamide (OptiMARK®), gadobenate dimeglumine (MultiHance®) and gadoteridol (ProHance®). Adverse reactions:

1. anaphylactic reactions: rare (prevalence: 0.03-0.1%)
2. nephrotoxicity: incidence is lower than with iodinated agents used with CT
3. **nephrogenic systemic fibrosis (NSF)**: a rare, but serious illness

characterized by fibrosis of skin, joints and other organs, which is associated with certain gadolinium containing agents given to patients with severe renal failure (most were on dialysis). ✖ Gadolinium is now relatively contraindicated with a GFR of 30-60 ml/min, and is contraindicated with GFR < 30[23]. Safest agents: Dotarem, Gadovist and ProHance[24]. Contrast agents with a linear structure appear to be associated with a higher risk of NSF and include: Omniscan, Multihance, Magnevist and OptiMARK. In patients with end-stage renal disease, the risk is ≈ 2.4% per gadolinium study[25]

4. gadolinium allergy: use the same allergy prep as for iodine allergy (*see page 124*)
5. for issues related to pregnancy, *see below*

CONTRAINDICATIONS TO MRI

An extensive reference[26] details safety issues. Web sites for MRI safety include: www.MRIsafety.com and www.IMRSER.org. Some issues that come up frequently in neurosurgical patients follows.

Pregnancy and MRI: During the first trimester, MRI can cause reabsorption of products of conception (miscarriage). There are no studies to determine the long term effects of MRI on a fetus after the first trimester (the low risk of MRI in this situation is probably preferable to the known dangers of ionizing radiation of x-rays (including CT)[27]). Gadolinium contrast is contraindicated during all of pregnancy, and is not approved for use in age < 2 years. Breast-feeding must be interrupted for 2 days after administration of gadolinium to the mother.

Contraindications to MRI:

1. cardiac pacemakers/defribrillator, implanted neurostimulators, cochlear implants, infusion pumps: may cause temporary or permanent malfunction
2. ferromagnetic aneurysm clips (*see below*): some centers exclude *all* patients with any type of aneurysm clip
3. metallic implants or foreign bodies with large component of iron or cobalt (may move in field, or may heat up)
4. Swann-Ganz catheter (pulmonary artery catheter)
5. metallic fragments within the eye
6. placement of a vascular stent, coil or filter within the past 6 weeks
7. shrapnel: BB’s (some bullets are OK)
8. relative contraindications:

A. claustrophobic patients: may be able to sedate adequately to perform study
B. critically ill patients: ability to monitor and access to patient are impaired. Specially designed non-magnetic ventilator may be required. Cannot use most brands of electronic IV pumps/regulators
C. obese patients: may not physically fit into many closed bore MRI scanners. Open bore scanners may circumvent this but many utilize lower field strength magnets and produce inferior quality images in large patients
D. non-MRI compatible metal implants in the region of interest (or previous surgery with high speed drills which may leave metal filings): may produce susceptibility artifact which can distort the image in that area
E. programmable shunt valve: (*see page 317*) most will tolerate up to a 3 T MRI without permanent damage, however, the pressure setting may be altered and therefore should be rechecked after having an MRI for any reason

Aneurysm clips and MRI

MRI considerations in patients with a cerebral aneurysm clip:

1. the danger of the MRI magnetic field causing the aneurysm clip to be pulled or torqued off of the aneurysm or to tear the neck
2. the artifact produced by the metal of the clip in the magnetic field
3. heat generated in the region of the clip: not clinically significant

Table 6-6 Magnetic remnance of aneurysm clips[28]

Clip	Type of steel	Magnetic remnance (no units)	MRI compatible?
Drake DR 12	martensitic SS	100	no
Heifetz	17-7PH	44	
Mayfield	martensitic SS	74	
Scoville	EN-58J	64	
Olivecrona		0	yes
Sugita	Elgiloy	0	
Sugita with loop	gold plated	1	
McFadden	Vari-Angle	0	
Yasargil	316	0	
Yasargil	Phynox	0	
Yasargil (old)		1	
silver clip		0	

The more ferromagnetic the clip, the larger the force exerted on it by the magnetic field and the greater the image distortion near the clip.

Stainless steel **(SS)** is classified as **martensitic** (ferromagnetic) or **austenitic** (non-ferromagnetic). Cobalt-based superalloys are non-ferromagnetic and include Elgiloy (Sugita clips), Phynox (Yasargil), and Vari-Angle (McFadden).

Table 6-6 shows the magnetic remnance of various clips which is related to their ferromagnetic properties. If in doubt at the time of aneurysm surgery, apply the following simple test: non-ferromagnetic clips cannot be lifted or dragged with a small magnet.

HEMORRHAGE ON MRI

Because its signal characteristics change with time (and location), blood is one of the most complex entities to interpret on MRI. A mnemonic for the changes in appearance of blood on MRI with time is shown in *Table 6-7*. For intracerebral hemorrhage, *see page 1125*. Blood, hemosiderin and calcium are dark on GRASS images. FLAIR is the best sequence for detecting SAH on MRI (*see page 129*).

Table 6-7 Signal characteristics of blood on MRI with time*

Time	T1WI	T2WI
Mnemonic	Acronym: “George Washington Bridge”	The layers of an Oreo® cookie
Acute	G (gray)	B (black)
Subacute	W (white)	W (white)

Chronic	B (black)	B (black)

* note: on T2WI blood is bright only in the sub-acute phase, and in the chronic phase it is dark on both T1WI & T2WI

6.4.2. Magnetic resonance angiography (MRA)

May be done with contrast (gadolinium, usually for extracranial vessels) or, without (usually for intracranial vessels, using flow related enhancement techniques (most commonly, 2D time of flight **(2D TOF)**)). Anything that appears bright on T1WI will also show up on MRA, but doesn't necessarily represent blood flow. This includes fat and fat-laden macrophages in an area of old CVA. Using fat-sat T1WI can mitigate this. Has some utility in screening for aneurysms (*see page 1038*), and for angiographically occult vascular malformations (*see page 1105*). High-flow AVMs are hard to resolve because arterialized veins can appear similar to arteries.

6.4.3. Diffusion-weighted imaging (DWI) and perfusion-imaging (PWI)

DIFFUSION-WEIGHTED IMAGING

Primary uses: early detection of ischemia and differentiating active MS plaques from old ones. DWI is sensitive to random Brownian motion of water molecules. Two images are generated, an apparent diffusion coefficient **(ADC)** map (based on a number of variables (time, slice orientation…)), and a trace image (the actual DWI)[29]. Freely diffusing water (e.g. in CSF) appears dark on DWI. ★ Parenchymal areas of bright signal on DWI may denote regions of restricted diffusion (abnormal).

The DWI is based on a T2WI, and anything that is bright on T2WI can also be bright on DWI ("**shine-through**"). Problem: bright areas on DWI can represent either restricted diffusion or T2 "shine-through". ∴ check the ADC map: if the lesion is black, then this likely represents true restricted diffusion (recent infarct is the most common etiology).

Differential diagnosis of areas of increased signal (bright) on DWI:

1. ischemic brain: acute stroke and areas with hypoperfusion (penumbra). While restricted diffusion usually indicates irreversible cell injury (death), it can some-times indicate tissue that is just near cell death (penumbra).

Acute brain ischemia can light up within minutes[29, 30]. The DWI abnormality will persist for ≈ 1 month. The ADC map usually normalizes after ≈ 1 week

2. cerebral abscess: DWI = bright, ADC = dark (*see page 352*)
3. active MS plaque (old plaques will not be bright)
4. some tumors: most tumors are dark on DWI, but highly cellular tumors (e.g. some meningiomas…) may have decreased diffusion (bright on DWI)

Other possible uses of DWI:

TIAs: some, but not all[31], are associated with DWI abnormalities. However, factors other than focal ischemia (e.g. global ischemia, hypoglycemia, status epilepticus…) can produce ADC decline and the DWI images must therefore be interpreted in relation to the clinical setting[29].

DWI may also be able to distinguish cytotoxic from vasogenic edema[32, 33] (*see page 109*

Perfusion-weighted MRI

Provides information related to the perfusion status of the microcirculation. PWI is the most sensitive study for ischemia of the brain (more sensitive than DWI) (FLAIR shows infarcted tissue). There are several methods currently in use; the bolus-contrast approach is the most widely employed[29]. Ultrafast gradient imaging is used to follow the gradual reduction to normal following administration of contrast (usually gadolinium). A signal wash-out curve is derived and is compared to contrast in an artery. In practical terms, PWI is not widely used because of technical challenges. Time-to-peak and mean-transit-time are 2 common parameters that are displayed (higher signal = longer times beyond normal).

DWI & PWI mismatch

DWI and PWI may be combined to locate areas of **diffusion-perfusion mismatch** (deficit on PWI that exceeds the zone of diffusion deficit on DWI), thus identifying salvageable brain tissue at risk of infarction ("**penumbra**", *see page 1062*) e.g. to screen for potential candidates for thrombolytic therapy[34].

6.4.4. Magnetic resonance spectroscopy (MRS)

This section specifically covers proton (H^+) MRS which can be performed on almost any MRI scanner (especially units ≥ 1.5 T) with the appropriate software. Spectroscopy of other nuclei (e.g. phosphorous) can be evaluated only with specialized equipment.

Table 6-8 Important peaks on proton MRS

Moiety	Resonance(ppm)	Description
lipid	0.5-1.5	slightly overlaps lactate peak at TE ≈ 35
lactate	1.3	a couplet peak. Not present in normal brain. End product of anaerobic glycolysis, ∴ a marker of hypoxia. Present in: ischemia, infection, demyelinating disease, inborn errors of metabolism… At higher TE (e.g. TE = 144), the peak inverts which can help distinguish it from the lipid peak
N-acetyl aspartate **(NAA)**	2	a neuronal marker. Normally the tallest peak (higher than Cr or Cho). ↓ in ≈ all focal and regional brain abnormalities (CVA, tumor, MS, epilepsy, Alzheimer's disease, abscess, brain injury…)
creatine **(Cr)**	3*	useful primarily as a reference for choline. Higher in grey matter than white matter
choline **(Cho)**	3.2	marker of membrane synthesis. ↑ in neoplasms and some rare conditions of increased cell growth & in the developing brain. ★ CVA is low in choline

* Cr has another less important peak

Single voxel MRS

A small area is selected on the "scout" MRI and the spectroscopic peaks for that region are displayed in resonance as a function of parts-permillion **(ppm)**. Since only small regions are selected, may be subject to "sampling" error.

Clinically important characteristic peaks are delineated in *Table 6-8*.

Illustrative patterns

Normal brain: *See Figure 6-1*.

Tumor: *See Figure 6-1*. ↓ NAA, ↑ lactate, ↑ lipid, ↑ choline (rule of thumb: with gliomas, the higher the choline, the higher the grade up to grade 3, thereafter necrosis reduces relative choline levels and the lipid peak may be utilized).

CVA: ↑ lactate peak predominates. Choline is characteristically low.

Abscess[35]: Reduced NAA, Cr & choline peaks, and "atypical peaks" (succinate, acetate…) from bacterial synthesis is pathognomonic for abscess (not always present). Lactate may be elevated.

Multiple sclerosis: Bland pattern. NAA slightly reduced. Lactate and lipid slightly elevated. Choline not elevated.

Possible uses of MRS

1. differentiating abscess from neoplasm
2. post-op enhancement vs. recurrence of tumor
3. distinguishing tumor from MS plaques: occasionally cannot be differentiated
4. in AIDS: may be able to help differentiate toxoplasmosis from lymphoma from PML (PML: ↓ NAA, no significant increase in choline, lactate or lipid)
5. the promise of differentiating tumor infiltration from edema has not materialized
6. some utility in distinguishing tumor from radiation necrosis (*see page 771*)
7. large inositol peak may distinguish hemangiopericytoma from meningioma[36])

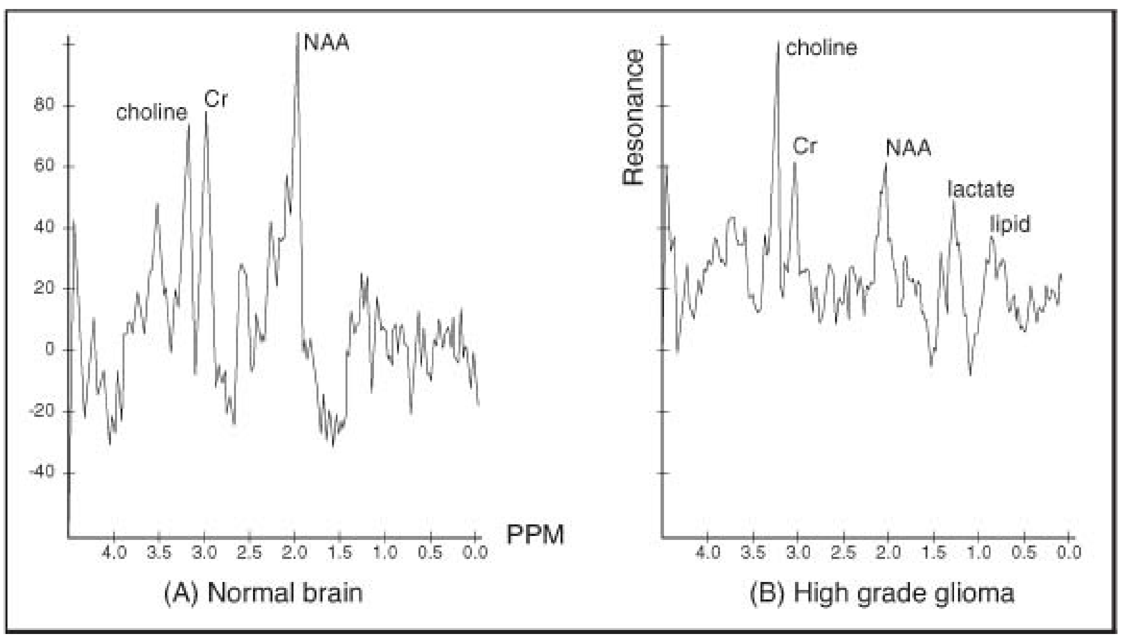


Figure 6-1 Proton MRS of (A) normal brain, and (B) high grade glioma

Multi-voxel MRS

Color coded scan with selected overlay for NAA, choline… one at a time. May reduce risk of sampling error.

6.4.5. Diffusion tensor tractography MRI (DTT)

An MRI technique that demonstrates white matter tracts by exploiting the difference in diffusion parallel to the tracts from diffusion perpendicular to their course.

Available only with specialized software for specific MRI scanners.

Contraindications are same as for MRI in general (*see page 130*).

Probably most useful to permit a surgeon to avoid critical white matter tracts during intraparenchymal brain surgery, especially when a lesion (e.g. tumor, AVM…) may displace these tracts from their expected position.

6.5. Angiography (cerebral)

Risks

Risk varies with the nature of the pathology being investigated and with the experience of the angiography team. Overall risk of a complication resulting in a permanent neurologic deficit[37, 38]: 0.1%. In ACAS, there was a 1.2% complication rate (*see page 1149*).

General information[39]

In general: non-vascular deep lesions cause changes in venous structures, superficial lesions affect arterial structures. The classic feature of a malignant neoplasm (e.g. glioblastoma) on angiography is an early draining vein. Meningiomas “come early, stay late” (appears early in arterial phase, blush persists beyond venous phase) - *see page 617* for other angiographic findings with meningiomas.

Allcock test: evaluates flow through the posterior communicating arteries by vertebral injection with simultaneous common carotid artery compression in the neck.

To help find the middle meningeal artery on lateral ECA angio, follow the anterior sweep of the sphenoid air sinus.

Intraoperative angiography

Typically used in aneurysm surgery to confirm exclusion of the aneurysm from

the circulation and to verify patency of critical adjacent vessels, and during AVM surgery to confirm total elimination of the nidus.

1. using traditional iodinated contrast and fluoroscopy. Requires use of radiolucent headholder. Typically the introducer sheath is placed in the femoral artery at the time of initial pre-op angio, and is left in place for intraoperative use
2. indocyanine green (ICG)[40, 41]: can be visualized under normal light, or sometimes to better advantage when illuminated with near-infrared light. Use is restricted to surface vessels. May be less reliable with giant or wide-neck aneurysms or with thick-walled atherosclerotic vessels[42]. Also used intraoperatively with some spinal AVMs

6.6. Plain films

6.6.1. C-Spine

NORMAL FINDINGS

For radiographic signs of cervical spine trauma, see *Table 28-7*, page 939, and for guidelines for diagnosing clinical instability, see *Table 28-30*, page 970.

CONTOUR LINES

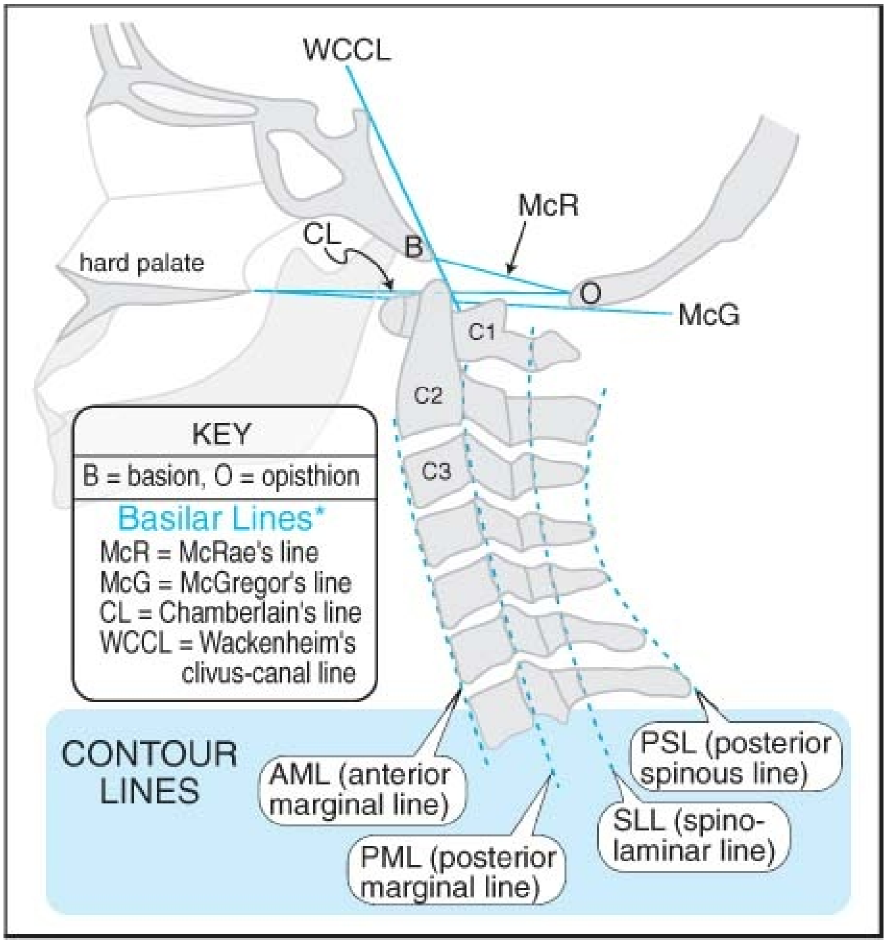


Figure 6-2 Spinal contour lines and lines used to diagnose basilar invagination Lateral view through craniocervical junction. *For a discussion of the basilar lines, see page 139

On a lateral C-spine x-ray, there are 4 contour lines (AKA arcuate lines). Normally each should form a smooth, gentle curve (*see Figure 6-2*):

1. posterior marginal line **(PML)**: along posterior cortical surfaces of vertebral bodies **(VB)**. Marks the anterior margin of spinal canal
2. anterior marginal line **(AML)**: along anterior cortical surfaces of VBs
3. **spinolaminar line (SLL)**: along base of spinous processes. The posterior margin of the spinal canal
4. posterior spinous line **(PSL)**: along tips of spinous processes

Relation of Atlas to Occiput

See *page 952* for criteria for atlantooccipital dislocation (AOD).

Relation of Atlas to Axis

These measurements are useful for atlantoaxial subluxation/dislocation e.g.

in trauma (*see page 957*) or rheumatoid arthritis (*see page 495*).

Rule of Spence

On AP or open-mouth odontoid x-ray, if the sum total overhang of both C1 lateral masses on C2 is **≥ 7 mm** (x + y in *Figure 6-7*), the transverse atlantal **(TAL)** ligament is probably disrupted[43, 44] (when corrected for an 18% magnification factor, it has been suggested that the criteria be increased to ≥ **8.2 mm**[45])

(Anterior) atlantodental interval (ADI)[A]

AKA predental space. The distance between the anterior margin of the dens and the closest point of the anterior arch of C1 (“C1 button”) on a lateral C-spine x-ray (*see Figure 6-3*). The normal maximal ADI is variously given in the range of 2 to 4 mm[46, 47]. Commonly accepted upper limits are shown in *Table 6-9*. An abnormally increased ADI is a surrogate marker for TAL disruption[48]

A. the term ADI usually refers to the *anterior* atlantodental interval (there is also a posterior ADI (*see page 495*) and a lateral ADI which can be seen on AP radiographs)

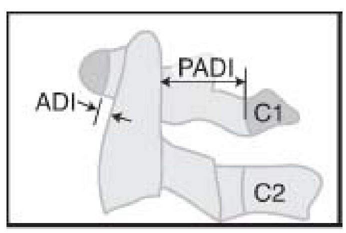


Figure 6-3 The atlantodental interval (ADI) and posterior atlantodental interval (PADI) on a lateral C-spine x-ray

Table 6-9 Normal ADI

Patient	ADI
adults	
males	≤ 3 mm
females	≤ 2.5 mm
pediatrics[49] (≤ 15 yrs)	≤ 4 mm

Posterior atlantodental interval (PADI)

AKA the neural canal width **(NCW)**[50]. The PADI is the AP diameter of the bony canal and is measured from the back of the odontoid to the anterior aspect

of the posterior C1 ring (*see Figure 6-3*). It is more useful than the ADI for some conditions (e.g. AAS in rheumatoid arthritis (*see page 495*) or Down syndrome (*see page 498*)).

Canal diameter

Normal canal diameter on lateral C-spine x-ray (from spinolaminar line **(SLL)** to posterior vertebral body with 6 foot tube to film distance)[51]: **17 ± 5 mm**. In the presence of osteophytic spurs, measure from the back of the spur to the SLL.

Cervical spinal stenosis: various cutoffs for the normal minimum AP diameter have been suggested[52]. On a plain lateral C-spine x-ray this is usually measured from the posterior vertebral body (or the posterior aspect of an osteophyte) to the spinolaminar line. Some use 15 mm. Most agree that stenosis is present when the AP diameter is **< 12 mm** in an adult (*see page 489* for correlation with myelopathy).

Prevertebral soft tissue

Abnormally increased prevertebral soft tissue **(PVST)** may indicate the presence of a vertebral fracture, dislocation, or ligamentous disruption[54]. Normal values for lateral C-spine x-ray and CT scan are shown in *Table 6-10*. Plain films are subject to errors due to magnification and rotation. Multi-detector CT **(MDCT)** eliminates these shortcomings[53].

Increased PVST is more likely with anterior than posterior injuries[55]. NB: the sensitivity of these measurements is only ≈ 60% at C3 and 5% at C6[54]. False positives may occur with basal skull/facial fractures, especially with fracture of the pterygoid plates.

An ET-tube may allow fluid to accumulate in the posterior oropharynx which can obscure this measurement. In this setting, one can look for a thin fat layer between the prevertebral muscles and the posterior pharynx on cervical CT; the prevertebral tissue (posterior to this line) will be thickened (no measurements available at this time). MRI can also demonstrate abnormal signal within the prevertebral tissue.

Table 6-10 Normal prevertebral soft tissue

Space	Level	Maximum normal width (mm)		
		Adults		Peds
		MDCT	Lateral X-Ray	
retro-pharyngeal	C1	8.5	10	unreliable
	C2-4	**6-7** *	**5-7**	
retrotracheal	C5-7	18	22	14

* CT data was deemed unreliable at C4[53]

INTERSPINOUS DISTANCES

C-spine AP: a fracture/dislocation or ligament disruption may be diagnosed if the interspinous distance is 1.5 times that at both adjacent levels (measured from center of spinous precesses)[56]. Also look for a malalignment of spinous processes below a certain level which may be evidence of rotation due to a unilaterally locked facet.

C-spine lateral: look for "**fanning**" or "**flaring**" which is an abnormal spread of one pair of spinous processes that may also indicate ligament disruption.

PEDIATRIC C-SPINE

C1 (ATLAS)

Ossification centers[57]: usually 3 (*see Figure 6-4*)

1. 1 (sometimes 2) for body (not ossified at birth; appears on x-ray during 1st yr)
2. 1 for each neural arch (appear bilaterally ≈ 7th fetal week)

Synchondroses[57]:

- synchondrosis of the spinous process: fuses by ≈ 3 yrs age
- 2 neurocentral synchondroses: fuse by ≈ age 7 yrs

Up to 5% of adults have incomplete closure of ossification centers of C1, most commonly posteriorly. The rare anterior defect is usually associated with a posterior defect.

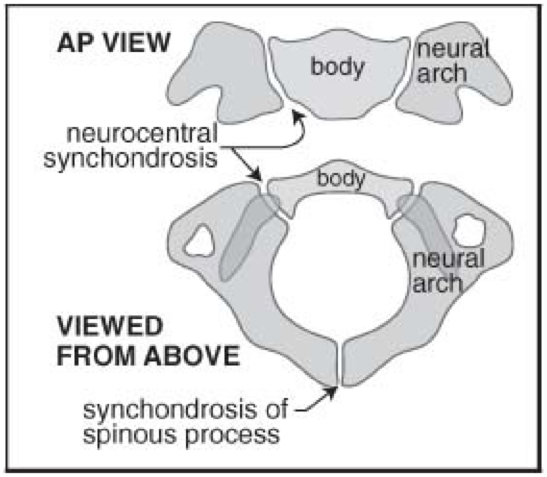


Figure 6-4 Pediatric C1 (atlas)

C2 (AXIS)

4 primary ossification centers (*see Figure 6-5*):

- odontoid process
- vertebral body
- 2 neural arches

Synchondroses: normally fuse between 3-6 years of age.

A secondary ossification center appears at the summit of the dens between 3-6 yrs, and fuses with dens by age 12[57].

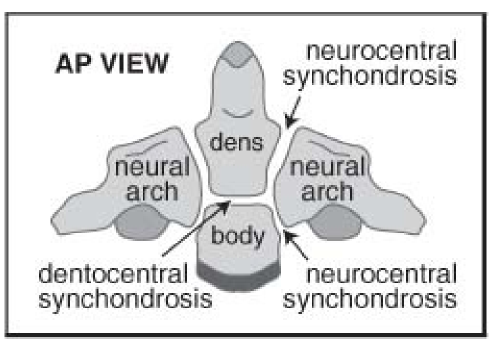


Figure 6-5 Pediatric C2 (axis)

C3-7

Cervical bodies are normally wedge shaped in pediatric population (narrower anteriorly). Wedging decreases with age.

6.6.2. Lumbosacral (LS) spine

L4-5 is normally the lumbar disc space with the greatest vertical height. Also see *Normal LS spine measurements*, page 480.

AP view: look for defect or non visualization of the “owl’s eyes” which is due to pedicle erosion which may occur with lytic tumors (common with metastatic disease).

Oblique views: look for discontinuity in neck of “Scotty dog” for defect in pars inter-articularis.

Butterfly vertebra: An uncommon congenital anomaly thought to arise from failure of fusion of the lateral halves of the VB due to persistent notochord tissue, producing a “butterfly” appearance on AP x-rays or coronal CT scan reconstructions. The involved VB is widened, and adjacent vertebrae may show a compensatory deformity as if to fill in some of the gap. May be associated with other spinal and rib malformations[58]. On lateral views may simulate compression fracture. In severe cases, there may be significant kyphosis and/or scoliosis. Often asymptomatic, requiring no treatment. May be associated with lipomyelomeningocele (*see page 251*).

6.6.3. Skull films

Water’s view: x-ray tube angled up 45° (perpendicular to clivus), AKA submental vertex view. **Towne’s view**: x-ray tube angled down 45°, to view occiput.

SELLA TURCICA

NORMAL ADULT DIMENSIONS ON SKULL X-RAY

Technique: true lateral, 91 cm target to film distance, central ray 2.5 cm anterior and 1.9 cm superior to EAM. *Table 6-11* shows normal values (*Figure 6-6* shows how measurements are made).

Depth **(D)**: defined as the greatest measurement from floor to diaphragma sellae.

Length **(L)**: defined as the greatest AP diameter.

Table 6-11 Normal sella turcica dimensions (*see Figure 6-6*)

Dimension	Max	Min	Ave
D (depth) (mm)	12	4	8.1
L (length) (mm)	16	5	10.6

ABNORMAL FINDINGS

Pituitary adenomas tend to enlarge the sella, in contrast to craniopharyngiomas which erode the posterior clinoids. Empty sella syndrome tends to balloon the sella symmetrically, and also does not erode the clinoids. Tuberculum meningiomas usually do not enlarge the sella, and may be associated with enlargement of the sphenoid sinus (sphenoid pneumosinus dilatans - *see page 1216*).

"J" shaped sella suggests optic nerve glioma. It can also occur congenitally in Hurler syndrome (a mucopolysaccharidosis).

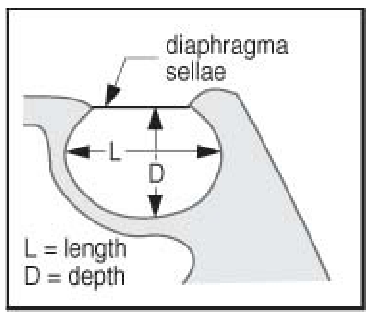


Figure 6-6 Measurements of the sella turcica (lateral view)

BASILAR INVAGINATION & BASILAR IMPRESSION (BI)

Terminology

The terms **basilar impression** and **basilar invagination** are often used interchangeably in the literature, and making a distinction seems pointless[A] (the abbreviation **(BI)** will be used for either). Common feature: upward displacement of the upper cervical spine (including odontoid process, AKA cranial migration of the odontoid) through the foramen magnum into the p-fossa.

A. historically, basilar invagination (AKA **cranial settling**) denoted upward indentation of skull base usually due to acquired softening of bone (*see below*), often associated with atlanto-occipital fusion, while basilar impression implied normal bone

Platybasia: flattening of the skull base. Originally assessed on plain x-rays (which are subject to error due to skull rotation or difficulty identifying landmarks), now more commonly evaluated on CT or MRI. May or may not be associated with BI, and may occur in association with craniofacial abnormalities, Chiari malformation, Paget's disease…

Quantitated by measuring the **basal angle**, which on plain x-rays, measured the angle between lines drawn from the nasion to center of sella and then to the anterior foramen magnum[59], but on MRI was felt to be better represented by the angle between a line drawn along the floor of the anterior fossa to the dorsum sellae and a second line drawn along the posterior clivus[60]. Normal mean basal angle: **130°**. Platybasia: **> 145°** (abnormally obtuse basal angle).

Measurements used in BI

(refer to *Figure 6-2*, page 135, and *Figure 6-7* below):

1. **McRae's line** ("McR" in *Figure 6-2*): drawn across foramen magnum (tip of clivus (basion) to opisthion)[61]. No part of odontoid should be above this line (the most accurate for BI). On CT[62] and MRI[63] the normal odontoid tip is 5 mm (± 1.8 mm) <u>above</u> the line
2. **Chamberlain's line** ("CL" in *Figure 6-2*)[64]: posterior hard palate to posterior margin of foramen magnum (opisthion). Less than 3 mm or half of dens should be above this line, with 6 mm being definitely pathologic. Seldom used because opisthion is often hard to see on plain film and may also be invaginated. On CT[62] and MRI[63] the normal odontoid tip is 1.4 mm (± 2.4) below the line
3. **McGregor's baseline** ("McG" in *Figure 6-2*)[65]: posterior margin of hard palate to most caudal point of occiput. No more than 4.5 mm of dens should be above this. On CT[62] and MRI[63] the normal odontoid tip is 0.8 mm (± 2.4) above the line
4. **Wackenheim's clivus-canal line** ("WCCL" in *Figure 6-2*): the odontoid should be tangential to or below the line that extends the course of the clivus (the clivus baseline). If the clivus is concave or convex, this baseline is drawn to connect the basion to the base of the posterior clinoids on the clivus[66]
5. **(Fischgold's) digastric line** ("FDGL" in *Figure 6-7*): joins digastric notches. The normal distance from this line to the middle of the atlanto-occipital joint is 10 mm (decreased in BI)[67]. No part of odontoid should be

above this line. More accurate than the bimastoid line (FBML)

6. **Fischgold's bimastoid line** ("FBML" in *Figure 6-7*): joins tips of mastoid processes. The odontoid tip averages 2 mm above this line (range: 3 mm below to 10 mm above) and this line should cross the atlanto-occipital joint

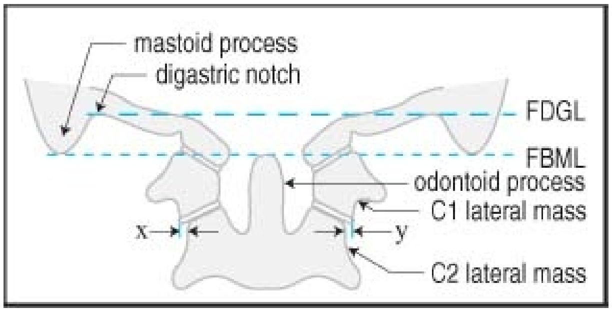


Figure 6-7 AP view through craniocervical junction*

* FDGL = Fischgold's digastric line, FBML = Fischgold's bimastoid line, x + y = total overhang of C1 on C2 (see Rule of Spence page 957)

Conditions associated with BI

1. congenital conditions (BI is the most common congenital anomaly of the craniocervical junction, it is often accompanied by other anomalies[68 (p 148-9)])
   A. Down syndrome
   B. Klippel-Feil syndrome: *see page 253*
   C. Chiari malformation: *see page 233* (in a series of 100 patients, 92 had BI[69])
   D. syringomyelia
2. acquired conditions
   A. rheumatoid arthritis (in part due do incompetence of transverse ligament, see *Basilar impression in rheumatoid arthritis*, page 497)
   B. post-traumatic
3. conditions with BI associated with softening of bone include[70]:
   A. Paget's disease
   B. osteogenesis imperfecta
   C. osteomalacia
   D. rickets
   E. hyperparathyroidism

Two subtypes of BI[71]

Type I: BI without Chiari malformation. Tip of odontoid tends to be above CL, McR, and WCCL in *Figure 6-7*. Brainstem compression is due to odontoid process invagination. 85% can be reduced with traction. Transoral surgery is recommended, usually accompanied by posterior fusion

Type II: BI + Chiari malformation. Odontoid tip tends to be above CL, but not McR or WCCL. Brainstem compression is due to reduced p-fossa volume. Only 15% can be reduced with traction. Foramen magnum decompression is appropriate

6.7. Myelography

Contraindications:

1. anticoagulation
2. allergy to iodinated contrast: requires iodine allergy prep (*see page 124*). NB: risk of adverse reaction still persists

Lumbar myelogram

Using iohexol (Omnipaque® 140 or 180) as shown in *Table 6-1*.

Cervical myelogram with water soluble contrast via LP

Use iohexol (Omnipaque® 300 or 240) as shown in *Table 6-1*. Insert spinal needle into lumbar subarachnoid space, tilt the head of the myelogram table down with the patient's neck extended and then inject dye. If a complete cervical block is seen, have patient flex neck. If the block cannot be traversed, patient may need C1-2 puncture or MRI (first obtain a CT which may show dye above the block that cannot be appreciated on myelography alone).

Post myelographic CT

Increases sensitivity and specificity of myelography (*see page 435*). In cases of complete block on myelogram, CT will often show dye distal to the apparent

site of the block.

6.8. Radionuclide scanning

Three phase bone scan

Technetium-99 (99mTc) pertechnetate is a radioisotope that may be attached to various substrates for use in bone scanning. It may be used to label polyphosphate (rarely used today), diphosphonate[72] **(MDP)**, or phosphorous (HDP) (the most widely agent used currently). Accumulates in areas of osteoblastic activity.

With technetium 99m-HDP, images are obtained immediately after injection (flow phase), at 15 min (blood pooling) and in 4 hours (bone imaging). Cellulitis shows up as increased activity in the first 2 phases, and there is little or diffuse increased activity in the 3rd. Osteomyelitis causes increased uptake in all 3 phases.

Used in evaluation of acute osteomyelitis with sensitivity and specificity of ≈ 95% each, and is usually positive within 2-3 days. False positives can occur in conditions involving increased bone turnover, e.g. fracture, septic arthritis, tumors. False negative can occur in cases with associated bone infarction.

Applications for bone scans include:

1. infection
    A. osteomyelitis of the spine (vertebral osteomyelitis, *see page 382*) or skull
    B. discitis: *see page 385*
2. tumor
    A. spine metastases: *see page 746*
    B. primary bone tumors of the spine: *see page 737*
    C. skull tumors: *see page 698*
3. diseases involving abnormal bone metabolism
    A. Paget's disease: of the skull (*see page 499*) or spine (*see page 499*)
    B. hyperostosis frontalis interna: *see page 701*
4. craniosynostosis: *see page 229*
5. fractures: spine (*see page 940*) or skull
6. "low back problems": to help identify some of the above conditions (*see page 432*)

Gallium scan

Nuclear medicine scan with 67Ga citrate which accumulates in areas of inflammation and some malignancies. Utility in neurosurgery for: sarcoidosis (*see* page 72), *chronic* vertebral osteomyelitis (for comparison to bone scan, *see* page 382).

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NOTES

7. Operations and procedures

This section provides information useful in the O.R. that apply to a number of different topics. Some items that are pertinent to only one topic will be found in that section instead (e.g. *transsphenoidal tumor removal* is found in the section on *pituitary tumors*).

REMEMBER: before performing any invasive procedure, know the patient's coagulation status (history, and if indicated: PT, PTT, bleeding time, platelets, FDP…).

7.1. Intraoperative dyes

This section covers visible dyes that may be useful in the operating room. For radioopaque dyes, see *Contrast agents in neuroradiology*, page 122. There is little information available in the literature regarding the intrathecal **(IT)** use of the following agents.

Indigo carmine: a blue dye which has been used intrathecally to locate CSF leaks. There are few published reports, and no accounts of adverse effects. In 1933 a report[1] of IT injection of 5 ml of 0.6% indigo carmine solution produced blue-green discoloration of the CSF draining through a fistula into the nose within 15 minutes, lasting for 5 hours, with no indication of toxicity. It is excreted in the urine (and not in mucous membranes). The consensus is that it should be relatively safe for IT use, but the manufacturer did not recommend this application.

✖ **Methylene blue**: methylene blue is probably <u>cytotoxic</u> and appears to become fixed to neural tissue. It should therefore <u>not</u> be used as a stain in neurosurgical operations or diagnostic tests. CNS damage (some permanent) occurred in 14 patients given an IT injection of a 1% solution. Symptoms included: paraparesis, quadriplegia, multiple cranial nerve involvement (including anosmia and optic atrophy), dementia and hydrocephalus[2].

Fluorescein: although intrathecal injection (e.g. to look for CSF leak) has been used by ENT surgeons with apparently acceptable results, there is a risk of

seizures. 2.5% fluorescein is diluted 1:10 with CSF or saline and ≈ 6 ml is injected into the spinal subarachnoid space (or 0.5 ml of 5% fluorescein mixed with 5-10 ml of CSF[3]).

Fluorescein has also been used IV (adult dose: 1 amp IV) to help mark areas where there is breakdown of the blood brain barrier (e.g. in tumors, *see page 109*), however, fluorescein is eventually excreted in mucus, urine, etc., and just about everything turns orange. It has also been used to perform intraoperative "visible angiograms" during the removal of AVMs.

Indigocyanine green (ICG): used for intraoperative angiography (*see page 135*).

7.2. Operating room equipment

OPERATING MICROSCOPE

Observer's eyepiece

For spine cases, the ideal location of the observer eyepiece is usually directly opposite the surgeon. For intracranial work, the observer's (assistant's) eyepiece is placed to right of operator's except in the following:

1. transsphenoidal surgery (when the surgeon stands to the patient's right)
2. right posterior fossa craniotomy in the lateral oblique (suboccipital) position

HEAD FIXATION

Indications for pin head-fixation:

1. ✖ not recommended for use in age < 3 years[A], use with care in age < 10 years
2. craniotomies:
   A. most intracranial vascular operations: radiolucent head-holder should be used if intraoperative angiogram is to be performed
   B. often for tumor operations
   C. when intraoperative image-guidance (IG) systems are used
3. cervical spine: often used for posterior cervical operations (laminectomies, instrumentation, fusions…)

A. this age cutoff is not based on scientific evidence, most reported complications occur in age > 3 years

Pin fixation devices include the Mayfield head-holder. Application:

1. "**skull block**" (blockade of scalp innervation) may be administered prior to pin placement. Critical for awake craniotomies (for the wake-up), and for vascular cases and cases with increased ICP where the block blunts the precipitous increase in blood pressure[4, 5] that may otherwise accompany pinning which may also increase ICP. For technique, *see page 151*
2. plan pin placement
   A. the manufacturer recommends that the pins be placed within a band-like area similar to a "sweatband" worn just above the orbits and the pinna
   B. avoid placing pins on the thin temporal squamosa, and use with caution over the frontal sinus[6]
   C. the single pin is typically placed anteriorly when the patient is in the supine position (see *Figure 7-7*, page 159), for a posterior fossa approach in the prone position, if the craniotomy is on one side the single pin is placed on that side
   D. the pins in the dual pin "rocker" should be equidistant from the centerline for maximal stability
3. appropriately sized sterile pins are placed in the head-holder:
   A. ✖ children < 3 yrs age[A]: increased risk of calvarial penetration or depressed skull fractures. A padded cerebellar head rest should be used instead[6, 7]
   B. children ≥ 3 yrs age and < 10 yrs age: special pediatric pins should be employed (with a "shoulder" to insure shorter depth of penetration)
4. the pins are often coated with appropriate antibiotic ointment
5. the clamp is squeezed together, allowing the ratchet gears to slide, until the pins are initially seated in the skull
6. the knob housing the tension spring and gauge is tightened (each ring = 20 lbs)
   A. adults: tighten until the **third ring (60 lbs)** is visible; up to 80 lbs has been described
   B. pediatrics: 30-40 lbs has been suggested[6]. ✖ Even with pediatric pins & decreased pressure, complications may occur, consider horseshoe

headrest

Complications of pin head-fixation:

1. malposition of pins:
   A. through unintended anatomic structures: pinna, orbit, superficial temporal artery, shunt hardware, prior craniotomy defect
   B. poor fixation by not properly placing pins close to "equator" resulting in movement during surgery (with risk of cervical spine injury, injury to structures being operated on due to the sudden movement, loss of image guided registration) and possible skin laceration
2. skin penetration by pins: can cause injury to intracranial structures, infection including delayed abscess, epidural hematoma[6]…
   A. overtightening of pins
   B. incorrect pin selection: *see above*
   C. soft skull: in elderly patients, poorly calcified skulls, pediatric patients[6]
3. skin necrosis: especially with pediatric pins due to the "shoulder" of the pins
4. skull fracture: including "ping-pong ball" fractures in young children
5. slippage of any of the joints or connections to the O.R. table
6. clamp breakage[8, 9]: inspect the head-holder for cracks prior to each application, store properly and maintain per the manufacturer's specifications
7. bleeding from pin site: usually when the head-holder is removed. If bleeding does not stop after a minute or so of pressure, a suture or surgical staple may be used

For rapid access or where stabilization is not critical, the head may be placed on a "doughnut" fashioned out of a rolled stockinette covered in plastic. Note: it actually only takes a few moments to apply pin fixation, and if there is any question about the possibility of e.g. a vascular lesion (AVM, etc.) it is worthwhile to have firm pin fixation, especially since many self-retaining retractors attach to the Mayfield head-holder.

7.3. Surgical hemostasis

Methods include:

1. thermocoagulation
   A. electrical coagulation:
      1. monopolar (Bovie) cautery: electric current passes through the patient to a grounding pad. Because of possible transmission through electrically and thermally sensitive neural structures, this modality is not used directly on the brain or in proximity to named nerves (including cranial nerves) & nerve roots
      2. bipolar cautery: current passes only between the tips of the cautery device. Used for precise coagulation. When used directly on or near to the brain or nerves, the current setting is typically reduced from that employed for general use
   B. thermal units: e.g. AccuTemp® disposable eye cautery units (particularly useful to coagulate dura when inserting a ventriculostomy in the ICU)
   C. laser: especially neodymium:yttrium-aluminum-garnet (Nd:YAG) laser
2. mechanical
   A. bone wax: originated by Sir Victor Horsely. Inhibits bone formation
   B. ligature: less commonly used in neurosurgery than other specialties
   C. "silver clips" (e.g. HemoClips®)
3. chemical hemostasis: *see below*

CHEMICAL HEMOSTASIS

See review[10] for more information. Some key points:

1. gelatin sponge (Gelfoam®): no intrinsic coagulating effect. Absorbs 45 times its weight in blood which causes it to expand and tamponade bleeding. Absorbable. May be combined with thrombin as patties or as powder (e.g. FLOSEAL®)
2. oxidized cellulose (Oxycel®) and oxidized regenerated cellulose (Surgicel®): absorbable. Acidic material that reacts with blood to form a reddish brown "pseudoclot". Bactericidal to over 20 different organisms. May retard bone growth. Oxycel® interferes with epithelialization more than Surgicel®
3. microfibrillar collagen (Avitene®): promotes adhesion and aggregation of platelets. Loses effectiveness in severe thrombocytopenia (< 10,000/ml). May be used on bone bleeding. Remove excess material to reduce risk of

infection

4. thrombin (Thrombostat®): does not depend on any intermediate physiological agent. Caution: although thrombin may cause significant edema when placed on brain where the pia has been disrupted, practical experience indicates this is uncommon

7.4. Craniotomies

7.4.1. Intraparenchymal cyst aspiration

When a cystic tumor or intracerebral hemorrhage is being operated on, an attempt should be made to insert a ventricular needle into the lesion and aspirate some but not all of the cyst contents. This often produces significant decompression. Avoid evacuating all of the contents otherwise the lesion might be difficult to find. The needle may then be left in place to allow localization of the lesion (or the needle track can be followed, which may occasionally be difficult).

7.4.2. Intra-operative brain swelling

Under certain circumstances during surgery, the brain may start to severely swell out of the craniotomy wound. Etiologies of this emergency situation include:

1. extraparenchymal bleeding: from a vessel or intraoperative aneurysm rupture, remotely situated epidural/subdural hematoma
2. intracerebral hemorrhage
3. venous outflow obstruction
4. vasodilatation induced by hypercarbia
5. severe diffuse cerebral edema following stroke or traumatic brain injury (TBI)

Management: First efforts should be aimed at ruling out and correcting the aforementioned causes as well as some adjunctive measures. Most maneuvers are similar to those used in controlling an ICP crisis. During the process, it is critical to try to avoid having the brain compress itself against the craniotomy bone edges which can lacerate the cortex and can also further compromise

cortical veins which impairs venous outflow causing more brain edema and swelling which accelerates the vicious cycle.

1. elevate the head of the patient (e.g. with reverse Trendelenburg of the O.R. table)
2. make sure the jugular veins are not kinked: this may require rotating the head by loosening the pivot that connects the table adapter to the Mayfield head holder and rotating the head to a more neutral position
3. rule-out hypercarbia: make sure the endotracheal tube is not kinked, check the patient's end-tidal pCO_2
4. measures to lower ICP and protect the brain
    A. give Mannitol 1 gm/kg IV bolus
    B. drain CSF if an option: from adjacent cistern or lumbar drain
    C. have anesthesiologist hyperventilate to a PCO_2 of 30-35 mm Hg
    D. have anesthesiologist induce burst suppression
5. emergently intubate patients who are undergoing awake craniotomy
6. consider intraoperative ultrasound if rapidly available to rule-out hematoma (intracerebral, EDH, SDH) which could potentially be immediately evacuated
7. during the above steps, place a moist sponge on the surface of the brain and gently but firmly apply evenly distributed pressure to push the brain back into the wound
8. if all else is failing, the craniotomy flap can be enlarged as much as possible to create a decompressive craniotomy. Enlarging the skin incision to do so is preferable to having too small a bony opening which risks brain compression/laceration against the edges. The skin is closed without the bone flap and without dural closure as in a decompressive craniectomy (*see page 165*)
9. a last ditch life-saving measure for continued uncontrollable swelling which is to be taken under advisement with eloquent cortex: use a gloved hand to sweep the herniating brain out of the wound (i.e. remove it from the patient)

7.4.3. Craniotomy pre- & post-op management

RISKS

Many risks cannot be generalized for all craniotomies and are specific to

various tumors, aneurysms, etc. General information:

1. post-operative hemorrhage
   A. overall risk of post-operative hemorrhage[11, 12]: 0.8-1.1%. 43-60% of the hematomas were intraparenchymal, 28-33% epidural, 5-7% subdural, 5% intrasellar, 8% mixed, 11% confined to superficial wound. Overall mortality was 32%
   B. hematoma may occur at the surgical site or in remote locations, e.g. intracerebellar hemorrhage after pterional[13] and temporal[14] craniotomies (*see page 1121*)
2. in craniotomy for brain tumor[15]:
   A. risk of anesthetic complications: 0.2%
   B. increased neurologic deficit in 1st 24 hours post-op: ≈ 10%
   C. wound infection: 2%
3. postoperative headache (*see page 149*)

PRE-OP ORDERS

1. for tumor: if patient on steroids, give ≈ 50% higher dose 6 hrs before and on-call to O.R. (stress doses); if not on steroids give dexamethasone 10 mg PO 6 hrs before and on call to O.R. (in A.M., give with sip water)
2. antiepileptic medication
   A. if there is a history of seizures:
      1. if already on antiepileptic drugs **(AEDs)** continue same doses
      2. if not on AEDs, load with Keppra 500 mg or oral PHT (may give 300 mg PO q 4 hrs **x** 3 doses (total 900 mg) to load orally)
   B. if no history of seizures
      1. if surgery does not require a cortical incision (e.g. aneurysm) then AEDs are generally not used
      2. if a cortical incision is anticipated, option to load with AEDs as above
3. prophylactic antibiotics: (*optional*) ideally 30-60 minutes before incision. For most antibiotics, it is given in the O.r.R before the skin incision. For antibiotics that take a long time to infuse (e.g. vancomycin) it may help to order it to be given "on call to O.R. "
4. DVT prophylaxis: pneumatic compression boots or knee-high TED® hose

POST-OP ORDERS

<u>Guidelines</u> (individualize as appropriate) for patient to be extubated

1. admit PACU, transfer to ICU (neuro unit if available) when stable
2. VS: q 15 min x 4 hrs, then q 1 hr. Temperature q 4 hrs x 3 d, then q 8 hrs. Neuro check q 1 hr
3. activity: bed rest (BR) with HOB elevated 20-30°
4. knee high TED hose or pneumatic compression boots
5. I & O q 1 hr (if no Foley: straight cath q 4 hrs PRN bladder distension)
6. incentive spirometry q 2 hrs while awake (<u>do not use following transsphenoidal surgery</u>)
7. diet: NPO except minimal ice chips and meds as ordered
8. IVF: NS + 20 mEq KCl/L @ 90 ml/hr
9. O_2: 2 L per NC
10. meds:
    A. dexamethasone (Decadron®): if not on chronic steroids, give 4 mg IV q 6 hrs. Otherwise give stress doses based on patients current dose and length of treatment (*see page 32*)
    B. H_2 antagonist, e.g. ranitidine 50 mg IVPB q 8 hrs
    C. Keppra® (levetiracetam): 500 mg PO or IV q 12 hours. Maintain therapeutic AED levels for 2-3 months post-op for most supratentorial craniotomies
    D. Cardene® drip: titrate to keep SBP < 160 mm Hg and/or DBP < 100 mm Hg (use cuff pressures, may use A-line pressures if they correlate with cuff pressures)
    E. codeine 30-60 mg IM q 3-4 hrs PRN H/A
    F. acetaminophen (Tylenol®) 650 mg PO/PR q 4 hrs PRN temperature > 100.5° F (38 C)
    G. *continue prophylactic antibiotics if used:* (e.g. cefazolin (Kefzol®) 500-1000 mg IVPB q 6 hrs x 24 hrs, then D/C)
11. labs:
    A. CBC once stabilized in ICU and q d thereafter
    B. renal profile once stabilized in ICU and q 12 hrs thereafter
    C. ABG once stabilized in ICU and q 12 hrs x 2 days, then D/C (also check ABG after any ventilator change if patient on ventilator)
12. call M.D. if any deterioration in crani checks, for T > 101° (38.5 C), sudden increase in SBP, SBP < 120, U.O. < 60 ml/2-hrs

POST-OP COMPLICATIONS

POSTOPERATIVE DETERIORATION

When the postoperative neurologic status is worse than pre-op, especially in a patient who deteriorates after initially doing well, emergency evaluation and treatment is indicated.

Possible etiologies:

1. hematoma (see *Risks*, page 147)
   A. intracerebral hemorrhage **(ICH)**
   B. epidural hematoma: at or remote from surgical site
   C. subdural hematoma
2. cerebral infarction
   A. arterial
   B. venous infarction: especially with surgery on or around the venous sinuses (e.g. *see page 171*)
3. postoperative seizure: may be due to inadequate anticonvulsant levels, and may be exacerbated by any of the above (*see below for management*)
4. acute hydrocephalus
5. pneumocephalus (also see *Pneumocephalus*, page 890):
   A. tension pneumocephalus: see *Tension pneumocephalus*, page 891
   B. simple pneumocephalus: the simple presence of air in the cranium can cause neurologic symptoms even if not under tension. Symptoms include: lethargy, confusion, severe headache, nausea & vomiting, seizures. Air may be located over the cerebral convexities, in the p-fossa, and/or in the ventricles and usually resorbs with symptomatic improvement in 1-3 days
6. edema: may improve with steroids
   A. worsening of cerebral edema: moderate post-op worsening of cortical function of immediately adjacent brain is not unexpected in many operations, and is usually transient. However, reversible etiologies (such as subdural hematoma) must be ruled out
   B. traction or manipulation of cranial nerves may cause dysfunction that may be temporary. Division of cranial nerves can cause permanent dysfunction
7. persistent anesthetic effect (including paralytics): unlikely in a patient who

deteriorates after initially doing well post-op. Consider reversing medication given during surgery (caution re hypertension and agitation), e.g. naloxone, flumazenil (*see page 281*), or reversal of pharmacologic muscle block (*see page 27*)

8. vasospasm: following SAH or may be due to manipulation of blood vessels

POSTOPERATIVE SEIZURES

Management:

1. intubate if patient does not rapidly regain consciousness, is not protecting airway, or has labored respirations
2. CT scan: rule out hematoma (intracerebral or extra-axial) or hydrocephalus
3. anticonvulsants:
   A. draw blood for appropriate anticonvulsant level
   B. bolus with additional anticonvulsants: do not wait for levels

POSTOPERATIVE HEADACHE

Persistent headache **(H/A)** is well described following posterior fossa craniectomy (incidence range: 0-83%[16]). The time course in one series[17] was: 23% at 3 mos, 16% at 1 yr, and 9% at 2 yrs.

Persistent H/A may also be observed following supratentorial craniotomy[18] (prevalence 1 year after anterior temporal lobectomy for seizures: 12%[18]). The "**syndrome of the trephined**": headache and sometimes pulsatile pain (usually localized to the area of the skull defect), amnesia, inability to concentrate, insomnia… similar in some ways to postconcussive syndrome (*see page 910*).

These H/A have been attributed to: traction on the dura when the bone is not replaced, tension on the dura due to tight dural closure, temporalis or nuchal muscle dissection, nerve entrapment in the closing sutures or in the healing scar, intradural blood and/or bone dust, CSF leak[18].

Prevention

No single method or group of methods has been successful in completely eliminating the complaint of post-op H/A[19, 20]. Until further research can further advance the understanding of the cause and prevention of these H/A, it seems reasonable to employ the following measures as much as possible in an attempt to minimize these debilitating symptoms: restoring function of the temporalis or

suboccipital musculature, rigid fixation of bone flaps, cranioplasty for large craniectomies, meticulous tension-free dural closure (using duraplasty when necessary), and keeping intradural blood clot and bone dust to the minimum possible[21]. Cranioplasty following posterior fossa surgery for vestibular schwannoma reduced the incidence of post-op H/A from 17% to 4%[22].

Treatment

Initially, symptomatic treatment is indicated. Referral to a H/A specialist may be appropriate when it becomes apparent that the H/A are not resolving spontaneously after ≈ 3 months[21].

7.4.4. Intraoperative cortical mapping (brain mapping)

Indications: typically used to locate motor strip, sensory cortex, or speech centers intraoperatively for surgery in and around these eloquent areas. Localization of these areas based on visible anatomy alone is unreliable. These techniques are typically employed in seizure surgery as well as in treating lesions in areas of eloquent brain.

Some techniques require an awake patient, with the surgery being done under local anesthesia with sedation. Motor and sensory cortex can also be localized in anesthetized patients using SSEPs (*see below*).

PHASE REVERSAL METHOD FOR LOCALIZING PRIMARY SENSORY AND MOTOR CORTEX

Utilizes intraoperative SSEPs to localize primary sensory and motor cortex in patients under general anesthesia (as opposed to using brain mapping techniques in awake patients)[23, 24].

Technique: For anesthesia requirements for intraoperative EP monitoring, *see page 4*. A strip grid is placed on the surface of the brain perpendicular to the anticipated orientation of the central sulcus. SSEP stimulation is performed while recording through the strip grid. Phase reversal of the N20/P20 peak between a pair of electrodes in the strip grid indicates that those electrodes straddle the central sulcus (*see Figure 7-1*) with primary motor cortex located anteriorly, and sensory cortex posteriorly. The grid is then repositioned and the test is run again to verify the findings.

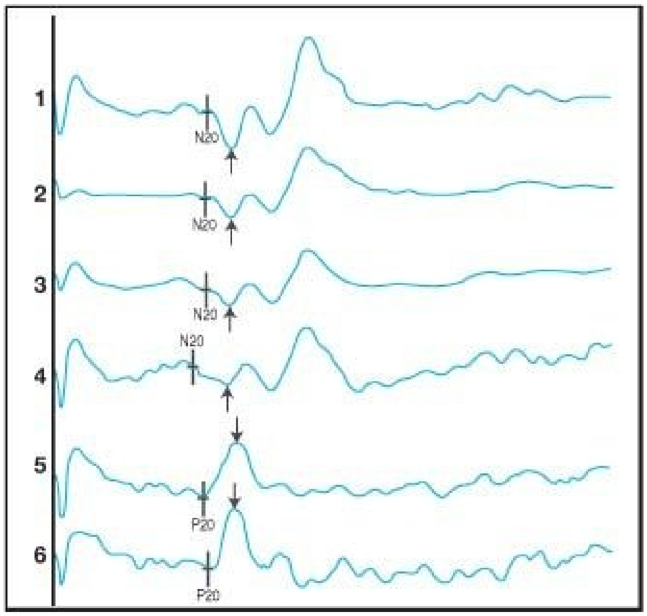

Figure 7-1 Phase reversal Intra-op 6-electrode recording strip placed on the brain during SSEP recording. Phase reversal of the negative N20 peak (arrows) to a positive P20 peak between electrodes #4 & $5 indicates that electrodes #4 & 5 straddle the central sulcus.

AWAKE CRANIOTOMY

Usually employed for brain mapping, especially for speech areas. Numerous techniques and protocols have been described. Typically, the patient is temporarily anesthetized with short acting agents (inhalational and/or injectable). This is supplemented with local anesthetic. The craniotomy is then performed and the patient is allowed to wake up while the brain is exposed to permit neurophysiologic testing during surgery. If (short-acting) paralytics are used, it is critical to reverse these agents 15-30 minutes prior to applying the electrical stimulation and that a train-of-four muscle twitch can be elicited.

Indications

1. surgery in eloquent brain (near motor strip (Brodmann's area 4 in *Figure 5-1*, page 84) or speech/language centers (Wernicke's & Broca's areas)) or thalamus, including tumors and epileptic foci
2. removal of brainstem tumors
3. some seizure surgery to look for seizure focus

Contraindications to awake craniotomy

1. patient unlikely to be able to cooperate: very young or very elderly

patients, confused patients, those with significant speech deficits already present or language barrier

Booking the case - awake craniotomy

Also see defaults & disclaimers (*page v*) and pre-op counselling (*see below*).

1. position: depends on lesion location, with pin headholder (for image guided navigation if used)
2. equipment:
   A. microscope if needed e.g. for tumor dissection
   B. image guided navigation system (if used)
   C. ultrasonic aspirator (for tumors)
3. anesthesia: pre-op consult for "awake craniotomy" & skull block
4. consult neurology or neuropsychology to be available during surgery for intra-op neurologic testing for "awake craniotomy"
5. EEG techs to perform intra-op EEG and provide brain stimulator
6. post op: ICU
7. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery on the brain to be performed with periods where the patient will be woken up for testing, (plus whatever else is planned, e.g. removal of tumor, removal of seizure source…)
   B. alternatives: the same surgery under general anesthesia, nonsurgical management, (for some diagnoses, e.g. tumor, radiation therapy)
   C. complications: (usual craniotomy complications: stroke, bleeding, coma, death, infection, seizures), difficulty accurately mapping the desired areas of the brain

Patient counselling pre-op

Patients need to be aware of what the sequence of events will be and what will be expected of them. It may be helpful to have them practice reading some typical material that will be used in the O.R. Patients over age ≈ 40 usually need reading glasses to see written material, and they should have their own available in the O.R., although the temples (earpieces) usually can't be accommodated. The patient should be advised that there may be some pain involved.

Patient positioning for surgery

Significantly more time must be spent on patient positioning to ensure that they will be as comfortable as possible without moving. Extra padding is employed. Access to the patient's face is necessary for the anesthesiologist and the neurophysiologist.

Typical sequence for anesthesia[204]

1. in the pre-op holding area, load with Precedex® (dexmedetomidine) 0.5 mcg/kg IV over 20 minutes followed by intra-op infusion at 0.4-1.0 mcg/kg/hr
2. induction of anesthesia utilizes propofol 3 mg/kg IV followed by laryngeal mask airway **(LMA)** placement
3. **skull block** 4: injection of local anesthetic (e.g. 30 ml of 0.5% bipuvicaine) to permit the skin incision and also rigid head fixation with pins (as required for image navigation devices, and situations where no head movement can be tolerated during surgery) without pain at the time of the wake-up. Injection at 4 regions on each side as shown in *Figure 7-2*:
   - ❶ supraorbital & supratrochlear nerves: 2 ml injected 1.5 cm above the supraorbital foramen above the medial third of the orbit
   - ❷ auriculotemporal nerve: 5 ml injected 1.5 cm anterior to the tragus. ✖ Caution: to avoid anesthetizing the facial nerve, inject just deep to the subcutaneous tissue

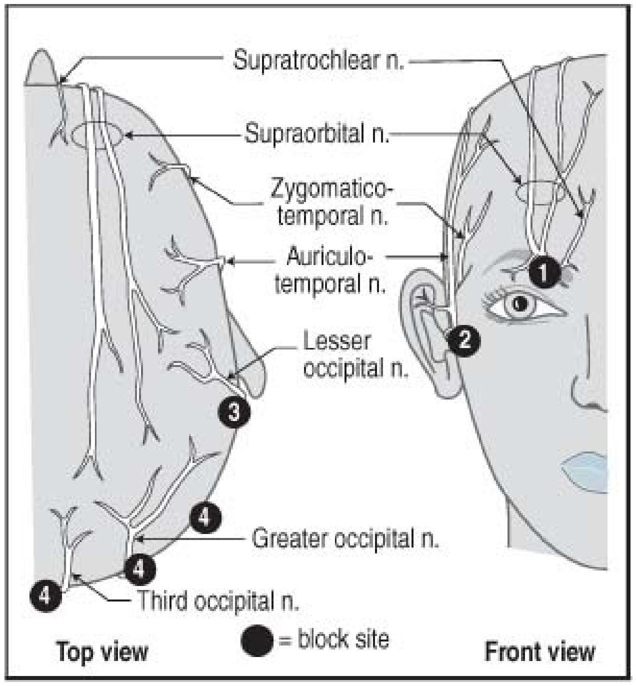

Figure 7-2 Infiltration sites for skull block

- ❸ postauricular branches of the greater auricular nerve: 2 ml 1.5 cm posterior to the antitragus
- ❹ greater, lesser & third occipital nerves: inject 5 ml with a 22 gauge spinal needle at the mastoid process and proceed along the nuchal ridge until the midline is reached

4. start inhalational anesthesia with 0.5 MAC desflurane with the patient breathing spontaneously while the scalp incision, craniotomy, and dural opening are performed (the dura is pain sensitive, the brain is not)
5. as the dural opening is begun, the desflurane is turned off and a remifentanyl infusion of 0.1-0.2 mcg/kg/min IV is started
6. by the time the dural opening is completed, the desflurane has usually worn off and the LMA can be removed
7. remifentanyl is then titrated for pain control
8. neurophysiologic testing can usually be performed at this time (e.g. see *Speech mapping* below)
9. the operation may often be carried to completion with the patient awake, although once the intracranial part of the operation is completed, more pain relief may be desired and general anesthesia may be needed for pain control or agitation (LMA may suffice here)

SPEECH MAPPING

Typical settings for a constant current generator using a bipolar electrode are shown in *Table 7-1*. If a voltage based unit is used, start at 1 volt and increase.

Speech mapping

There are numerous methodologies. One protocol:

1. requires awake craniotomy
2. once temporal lobe is exposed, a recording electrode strip is place on the brain surface
3. using a bipolar stimulator, start with a low current (e.g. 2 mA) and begin stimulate an area of cortex for 3-5 seconds, and observe for afterdischarges (akin to a focal seizure) on the recording strip. If no afterdischarges, in crease the current in 2 mA increments up to a maximum of ≈ 10 mA. If afterdischarges occur, back off by 1-2 mA and then test that area for speech changes as follows
4. stimulate cortex while patient names objects shown on picture cards (automatic verbalization, such as counting, is robust and may persist). Observe for effects ranging from total speech arrest to paraphasic errors
5. repeat the above steps at the next area (first finding threshold for afterdischarges and then stimulating while testing)

Table 7-1 Settings for constant current generator

Control	Setting*
frequency	50-60 Hz
waveform	biphasic square wave
duration	2-4 mS peak-to-peak
mode	repeat
polarity	normal
current	varies between 2-16 mA

* not all settings are present on all models

7.4.5. Posterior fossa (suboccipital) craniectomy

INDICATIONS

To gain access to the cerebellum, cerebellopontine angle **(CPA)**, to one vertebral artery, posterior brainstem, fourth ventricle, pineal region, or, using extreme lateral posterior fossa approach to the anterolateral brain stem. See paramedian (*page 154*) and midline (*page 156*) suboccipital craniectomies for details.

TECHNIQUE

POSITION

Position options include:

1. sitting position: *see below*
2. lateral oblique: patient three-quarters oblique (almost prone), *see page 154*
3. semi-sitting
4. supine with shoulder roll, head almost horizontal
5. prone
6. Concorde position: prone, thorax elevated, neck flexed and tilted away from the side on which the surgeon will be standing

SITTING POSITION

Used less frequently than in the past because of associated complications and acceptable alternative positions (except for some specific circumstances). However, some experts feel that the risks of the sitting position have been greatly overstated[25].

Advantages

1. improved drainage of blood and CSF out of surgical site
2. enhanced venous drainage which helps reduce venous bleeding and also ICP
3. easy ventilation due to unencumbered chest
4. patient's head may be kept exactly midline, aiding operator orientation, and reducing risk of kinking of vertebral arteries

Disadvantages/risks

1. possible air embolism (*see below*)
2. fatigue of operators hands
3. increased surgical risks from placement of CVP catheter (required to treat

possible AE): e.g. pneumothorax with subclavian vein catheterization, thrombosis

4. risk of post-op hematoma at the operative site may be increased since potential venous bleeders may remain occult while the patient is sitting, but may manifest when patient returns to a horizontal position post-op. However, one study found no such increased incidence[11]
5. risk of post-op subdural hematoma: 1.3% of p-fossa cases[26]
6. possible brachial plexus injury: prevent this by not allowing patient's arms to hang at the side. Instead, fold them across abdomen
7. midcervical quadriplegia[27, 28]: presumably due to flexion myelopathy[29-31]. The combination of the sitting position with hypotension[32] or neck flexion with possible compression of the anterior spinal artery, ± cervical bar, and elevation of the head thus reducing the arterial pressure may all contribute
8. sciatic nerve injury (**piriformis syndrome**)[33]: prevent this by flexing patient's knees (reduces tension on sciatic nerve)
9. extent of post-op pneumocephalus is more pronounced, and may increase the risk of tension pneumocephalus[34] (see *Pneumocephalus*, page 890)
10. venous pooling of blood in the LEs under anesthesia may cause relative hypovolemia and should be counteracted by binding the LEs prior to positioning
11. decreased cerebral blood flow due to lower hemodynamic arterial pressure[35]

Air embolism (AE): A potentially fatal complication of any operation when an opening to air occurs in a non-collapsible vein (e.g. diploic vein or a dural sinus) when there is a negative pressure in the vein (e.g. when the head is elevated above the heart)[36]. Air is entrained in the vein and can become trapped in the right atrium which may impair venous return causing hypotension. May also produce cardiac arrhythmias. **Paradoxical air embolism** can occur in the presence of a patent foramen ovale[37] or pulmonary AV fistula, and may produce ischemic cerebral infarction.

Greater negative pressures occur in the sitting position due to the extreme elevation of the head, but AE can occur in any operation with the head elevated higher than the heart. Incidence: a wide range has been quoted in the literature, and depends on the monitoring method used: ≈ 7-25% incidence with the sitting position using Doppler monitoring is an estimate[26].

Operations with significant risk of AE[A] require the use of a right atrial CVP

line (to aspirate air), and monitoring for air embolism; options include: transesophageal echo (the most sensitive), precordial Doppler monitoring.

A. although technically the risk of air embolism includes any case where the head is higher than the right cardiac atrium, practically it is limited to cases where the head of the bed is ≈ > 30° which is mostly limited to the sitting position for posterior fossa tumors

Table 7-2 Treatment for air embolism

1. find and occlude site of air entry, or else rapidly pack wound with sopping wet sponges/laps and wax bone edges
2. lower patient's head if at all possible (30° or less from horizontal)
3. jugular venous compression (bilateral best; second choice: right only)
4. rotate patient <u>LEFT</u> side down (attempt to trap air in right atrium)
5. aspirate air from right atrium via CVP catheter
6. ventilate patient with 100% O_2
7. discontinue nitrous oxide if used (may expand AE)[38]
8. use pressors and volume expanders to maintain BP
9. PEEP is <u>ineffective</u> in preventing or treating AE; may increase the risk of paradoxical AE[36]

Diagnosis and treatment:

The earliest clue to the occurrence of AE may be a fall in the end tidal pCO_2. On TE an air bubble will be visualized. Machinery sounds in the precordial Doppler also suggest AE. Hypotension may develop. Measures shown in *Table 7-2* should be immediately instituted.

Lateral oblique position

AKA "**park bench**" position. Axillary roll for the down side arm (*see Figure 7-3*) (or, position the patient so that the down side arm extends over the edge of the table and is held in place by a sling formed by the Mayfield table attachment with copious padding). Upper arm supported on pillows or towels (avoid using a Mayo stand which restricts the ability to laterally tilt the OR table during surgery). Elevate thorax 10-15°. Tilt the vertex of the head towards the floor (*see below*). Optional spinal drainage (usually for large tumors). Pillow between the legs.

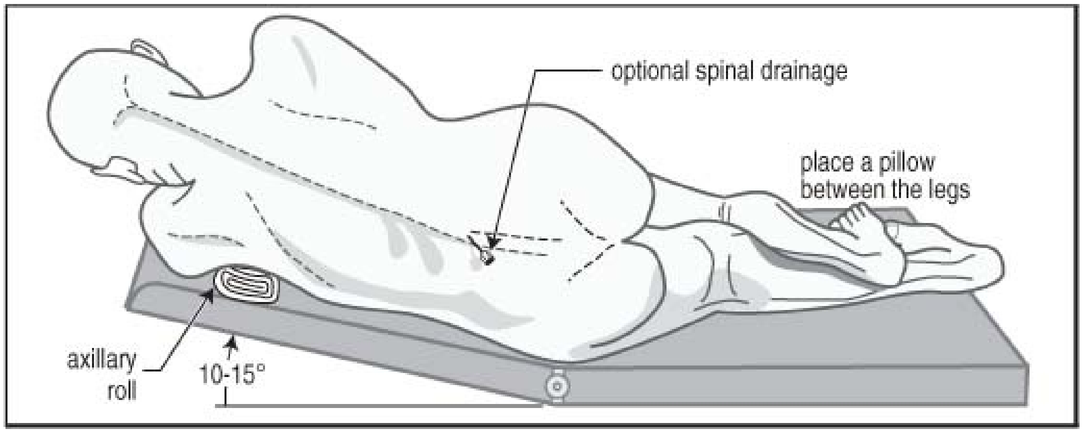

Figure 7-3 Lateral oblique ("park bench") position

For access to the porus acusticus or more caudally

(e.g. for vestibular schwannomas; not necessary for microvascular decompression for trigeminal neuralgia).

Get the shoulders out of the way by flexing the neck as much as possible while maintaining patent airway (aided by use of non-kinking wire-reinforced ET tube, so-called "**armored tube**"). The upper shoulder is retracted caudally by adhesive tape (avoid excess traction which may injure brachial plexus).

Head positioning

A Mayfield head-clamp is placed with the single pin on the side of the lesion, slightly anterior to a true-lateral on the skull, *see Figure 7-4*). The head is then rotated 20-30° face-down from the horizontal.

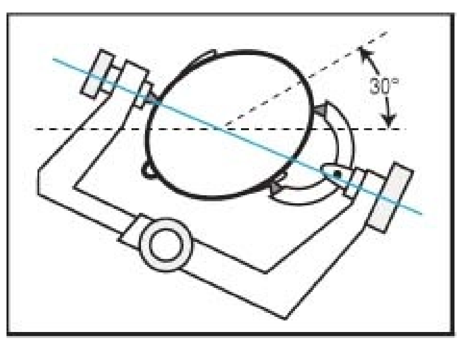

Figure 7-4 Position of head and head-holder for right suboccipital craniectomy (looking down on top of patient's head)

PARAMEDIAN SUBOCCIPITAL CRANIECTOMY

Indications:

1. access to the cerebellopontine angle **(CPA)**
   A. CPA tumors, including:
      1. vestibular schwannoma
      2. CPA meningioma
      3. epidermoid
   B. microvascular decompression
      1. trigeminal neuralgia
      2. hemifacial spasm
      3. miscellaneous: geniculate neuralgia, glossopharyngeal neuralgia
2. lesions of one cerebellar hemisphere:
   A. tumors: metastases, hemangioblastomas…
   B. hemorrhage within cerebellar hemisphere
3. access to vertebral artery
   A. aneurysms: PICA, vertebrobasilar junction
   B. vertebral endarterectomy
4. access to anterolateral brainstem tumors (extreme lateral p-fossa approach)
   A. foramen magnum tumors, including: chordomas, meningiomas

POSITION

Alternatives are listed on page 152. See page 154 for lateral oblique position.

SKIN INCISION

Linear (paramedian) incisions

Access to CPA. For microvascular decompressions and small CPA tumors, a linear incision provides adequate exposure and involves less trauma to overlying muscles, and may be easier to get watertight closure than with midline incision. For all of the following, the linear skin incision is located 5 mm medial to the mastoid notch (a palpable land-mark), (*see Figure 7-5*):

1. "5-6-4" incision (incision placed 5 mm medial to mastoid notch, extending from 6 cm above notch to 4 cm below). High enough to expose transverse sinus:
   • for approach to fifth nerve: microvascular decompression for trigeminal neuralgia
2. "5-5-5" incision (5 mm medial, extending 5 cm up to 5 cm down), used for approach to seventh/eighth nerve complex:

• microvascular decompression for hemifacial spasm
• small vestibular schwannoma

3. "5-4-6" incision (5 mm medial, extending 4 cm up to 6 cm down): used for approach to lower cranial nerves:
   • glossopharyngeal neuralgia

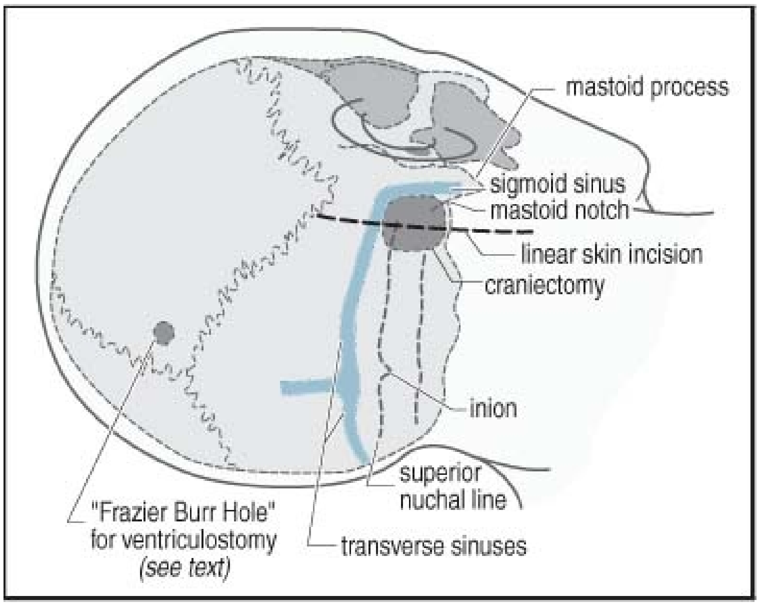

Figure 7-5 Paramedian suboccipital craniectomy

"Hockey-stick" incision

Useful for cerebellar hemispheric lesions as well as for larger CPA lesions where getting the muscles out of the way will facilitate maneuvering instruments about the posterior fossa.

Incision is made in the mid-line starting at ≈ C2 spinous process, proceeding superiorly to just above the inion, and then laterally to just beyond the mastoid tip (*see Figure 7-6*). A short optional caudal curve may be made laterally to further remove the muscle from the operative field.

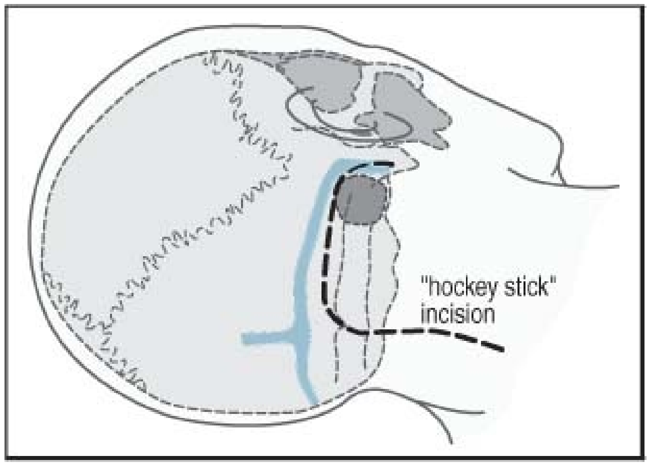

Figure 7-6 "Hockey-stick" skin incision

Craniectomy

Landmarks

The location of the inferior margin of the transverse sinus is quite accurately estimated at two finger-breadths above the upper limit of the mastoid notch (usually just above the superior nuchal line). This should be the upper limit of the skull opening.

For <u>small</u> tumors (< 2.5 cm)

May be done through craniectomy of ≈ 4 cm diameter placed in the angle between transverse and sigmoid sinuses.

For <u>large</u> tumors

A larger craniectomy may be needed, the size of which is limited by:

- transverse sinus superiorly
- foramen magnum inferiorly (which may be opened as prophylaxis against tonsillar herniation in the event of p-fossa edema post-op)
- sigmoid sinus laterally (opening mastoid air cells is acceptable, but to prevent CSF leak, these must be packed with bone wax and muscle (or bone dust from craniectomy[39]), and may be covered with reflected dura or fascia)
- midline medially (unless the tumor extends across the midline)

For approach to lower cranial nerves

(e.g. for glossopharyngeal neuralgia).

Craniectomy is extended inferiorly to ≈ 1/2 cm above foramen magnum.

Burr hole for emergency ventriculostomy

Optionally placed prophylactic occipital burr hole (**Frazier burr hole**) usually for intraparenchymal cerebellar tumors or any situation where post-op swelling or hydrocephalus is likely (not commonly used for microvascular decompression or small vestibular schwannomas).

Location: 3-4 cm from midline. In adults, 6-7 cm above the inion[40]; in pediatrics, 2-3 cm above the transverse sinus[41] (p 429) (i.e. ≈ 3-4 cm above the inion).

See *Post-op management* below for use.

Approach to the CPA

The angle of approach determines which portion of the posterior fossa is visualized.

- retracting the cerebellum <u>inferiorly</u> (working in the junction of the tentorium and petrous bone) gives access to the region of the trigeminal nerve, e.g. for microvascular decompression for trigeminal neuralgia
- <u>medial</u> retraction gains access to the region of the porus acusticus, e.g. for vestibular schwannomas
- <u>superior</u> retraction gains access to the lower cranial nerves, e.g. for geniculate neuralgia

MIDLINE SUBOCCIPITAL CRANIECTOMY

Indications: access to the midline or both sides of the posterior fossa

1. midline posterior fossa lesions
   A. cerebellar vermian and paravermian lesions, including: vermian AVM, cerebellar astrocytoma near the midline
   B. tumors of the fourth ventricle: ependymoma, medulloblastoma
   C. pineal region tumors
   D. brainstem lesions: brainstem vascular lesions (e.g. cavernous angioma)
2. decompressive craniectomies
   A. for Chiari malformation

3. cerebellar tumors: metastases, hemangioblastoma, pilocytic astrocytoma…

Position

For positioning, *see page 154*.

Skin/fascia incision

Midline incision from ≈ 6 cm above inion to ≈ C2 spinous process. Take the incision a little higher if a Frazier burr hole is to be done (can then utilize the same skin incision). The skin incision should leave the muscles and fascia intact. It is often difficult to place Raney clips on the skin in this region. To facilitate water-tight closure, the fascia is "T'd" at the top, leaving a cuff of tissue on the occiput just above the superior nuchal line.

Craniectomy

Craniectomy implies removal of bone (often piecemeal) with no intention of replacing it. Although craniotomy with replacement of bone flap at end of procedure has been used successfully, there is some concern that if there is post-op swelling, the inelastic bone flap may cause more pressure to be transmitted to the brain stem.

Usually taken down to foramen magnum. For cerebellar hemisphere tumors, many remove the posterior arch of C1 (caution re vertebral arteries on superior aspect of C1).

Approach

A "Y" shaped durotomy is often used. If the lesion has a cystic component, aspiration through a ventricular needle is used to partially decompress it.

Extreme lateral posterior fossa approach

Allows access to anterolateral region of brain stem. Differs from above in that the skin incision is designed to get the bulk of the skin and muscle flap out of the way.

Key: remove the lip of the foramen magnum as far laterally as possible, best done with a diamond drill.

Cranioplasty for suboccipital craniectomy

Methylmethacrylate cranioplasty as part of the closure following suboccipital crani for vestibular schwannoma reduced the incidence of post-op H/A from 17% to 4%[22].

POST-OP CONSIDERATIONS FOR P-FOSSA CRANI'S

POST-OP CHECK

In addition to routine, the following should be checked:

❑ 1. respirations: rate, pattern (see *Intubation* below)

❑ 2. follow closely for hypertension (*see below*)

❑ 3. evidence of CSF leak through wound

POST-OP MANAGEMENT

Intubation

Post-op intubation for 24-48 hours is sometimes maintained on a precautionary basis: many complications often have respiratory arrest as the initial manifestation (*see below*), and the patient may deteriorate precipitously from this point. There is a trade-off as the stimulus of the endotracheal tube may exacerbate hypertension and patient agitation, and so sedation is often required, which may obscure the neuro exam and depress respirations. If the patient wakes up extremely well from an uncomplicated p-fossa crani and it is not late at night, most surgeons will extubate.

Hypertension

Hypertension should be avoided at all costs to prevent bleeding from tenuous vessels (e.g. nitroprusside should be prepared prior to termination of the operation, and should be hanging and ready to titrate to keep SBP $\leq$ 160 mm Hg during the reversal of anesthesia and post-op).

Physician should be called for any sudden changes in BP post-op (may indicate elevated pressure in posterior fossa, *see below*).

POST-OP COMPLICATIONS

Posterior fossa edema and/or hematoma

In the posterior fossa, a small amount of mass effect can be rapidly fatal due to the paucity of room and the immediate transmission of pressure directly to the brain stem. It can also occlude CSF circulation through the aqueduct and cause acute hydrocephalus with the attendant risk of tonsillar herniation. Increased pressure in the p-fossa is usually heralded by sudden increases in BP or changes

in respiratory pattern (pupillary reflexes, level of consciousness and ICP are not affected until late). See *Table 7-3* for emergency treatment measures.

To expedite ventricular taps, a prophylactic occipital burr hole (**Frazier burr hole**) is often placed during posterior fossa surgery to permit drainage of CSF from the lateral ventricles in the event of acute hydrocephalus from blockage of the 4th ventricle or aqueduct. If acute hydrocephalus develops (e.g. from a hematoma), an emergent percutaneous ventricular tap with ventricular needle (or, if not available, spinal needle) is performed, passing the needle through the burr hole aiming for the middle of the forehead. In the presence of acute hydrocephalus, CSF should be encountered at a depth of 3-5 cm. NB: this maneuver may provide a few more minutes while preparing for the definitive treatment of reopening the wound; however, hydrocephalus may not initially be present since it takes some time to develop.

Table 7-3 Emergency treatment for p-fossa swelling

★ Rapid intubation, ventricular tap (through previously placed burr hole, if possible, *see below*), and reoperation is indicated. The wound should be opened immediately wherever patient is (recovery room, ICU, floor…). CT scanning may cost valuable minutes; it is rarely appropriate to delay treatment for this (must be judged on an individual basis).

CSF fistula

Occurs in 5-17% of cases. A potential source of meningitis, thus CSF leak must be treated immediately.

Etiologies: controversial. May include:

1. abnormal CSF hydrodynamics (i.e. hydrocephalus). Maneuvers to stem the leak will likely fail until the CSF is shunted or hydrodynamics normalize
2. poor wound closure: probably blamed more often than it is the actual cause
3. subarachnoid scarring

May be associated with meningitis (aseptic or infectious), multiple operations. Formation may be facilitated by coughing/sneezing, postural changes, one-way ball-valve mechanism due to a tissue flap.

An external CSF leak may occur through:

1. the skin incision
2. via the eustachian tube (*see* *page 630* for possible routes of egress

following sub-occipital vestibular schwannoma removal):
   A. through the nose (CSF rhinorrhea)
   B. down the back of the throat
3. the ear (CSF otorrhea) in cases with perforated TM

Treatment:

Initial treatment measures to temporize in the hope that CSF hydrodynamics will normalize and/or that the leak site will scar closed within a few days:

1. elevate the HOB
2. lumbar subarachnoid drainage
3. if the leak occurs through the skin incision:
   A. reinforce the incision with sutures, e.g. running locked 3-0 nylon after preparation of the skin with antimicrobial and local anesthetic
   B. alternatively, the incision may be painted with several coats of collodion

If persistent, a CSF fistula requires surgical correction, see *CSF fistula (cranial)*, page 300 for general information, *see page 631* for CSF fistula following suboccipital removal of vestibular schwannoma.

Suboccipital pseudomeningocele: An "internal" CSF fistula. Incidence following suboccipital craniectomy: 842-28%[43].

May be asymptomatic, but also may be associated with H/A, nausea/vomiting, local pain/tenderness. Some are soft and compressible, others may be tense.

Treatment options (up to 67% require permanent CSF drainage[44]):

1. noninvasive measures: expectant management, fluid restriction, head wrapping, keeping HOB elevated, acetazolamide. Steroids may be used if aseptic meningitis is suspected
2. percutaneous aspiration: "tap and wrap"[41 p 436, 45]. Risks introducing bacteria, causing infection
3. direct surgical exploration with multilayer re-closure[41 p 436]
4. lumbar drain: effective only if pseudomeningocele communicates with the subarachnoid space. ✖ May produce acute posterior fossa syndrome (H/A, nausea, vomiting, ataxia…)[42] especially if the pseudomeningocele doesn't communicate. Symptoms usually resolve with prompt discontinuation of lumbar drainage[42, 43]. Other potential complications: vagal nerve palsy, tonsillar herniation, subdural hematoma, kinking of PCA → stroke.

Drainage options:

A. external drain (temporary)

B. lumboperitoneal shunt (permanent)

5. ventricular drainage

   A. EVD (temporary)

   B. shunt (permanent)

Fifth or seventh nerve injuries

Causes diminished corneal reflex with potential corneal ulceration; initially managed with isotonic eye drops (e.g. Natural Tears®) q 2-4 hrs & PRN, or with a moisturizing insert (e.g. Lacricert®) q day, and at night with an eye patch or taping eyelid shut.

Miscellaneous

Supratentorial intracerebral hemorrhage has been described, and may result from transient hypertension[46].

7.4.6. Pterional craniotomy

INDICATIONS

1. aneurysms
   A. all aneurysms of anterior circulation
   B. basilar tip aneurysms
2. direct surgical approach to cavernous sinus
3. suprasellar tumors
   A. pituitary adenoma (when there is a large suprasellar component)
   B. craniopharyngioma

TECHNIQUE

POSITION

- supine, ipsilateral shoulder roll if head turned > 30° (*see below*)
- elevate thorax 10-15°: reduces venous distension
- flex knees

• Mayfield 3 pin head-holder: applied between true AP and true lateral (so that it is ≈ horizontal when head is rotated to the necessary position, *see Figure 7-7*)
• neck extended 15°: allows gravity to retract frontal lobe away from skull base
• head rotated from vertical as shown in *Figure 7-7*:

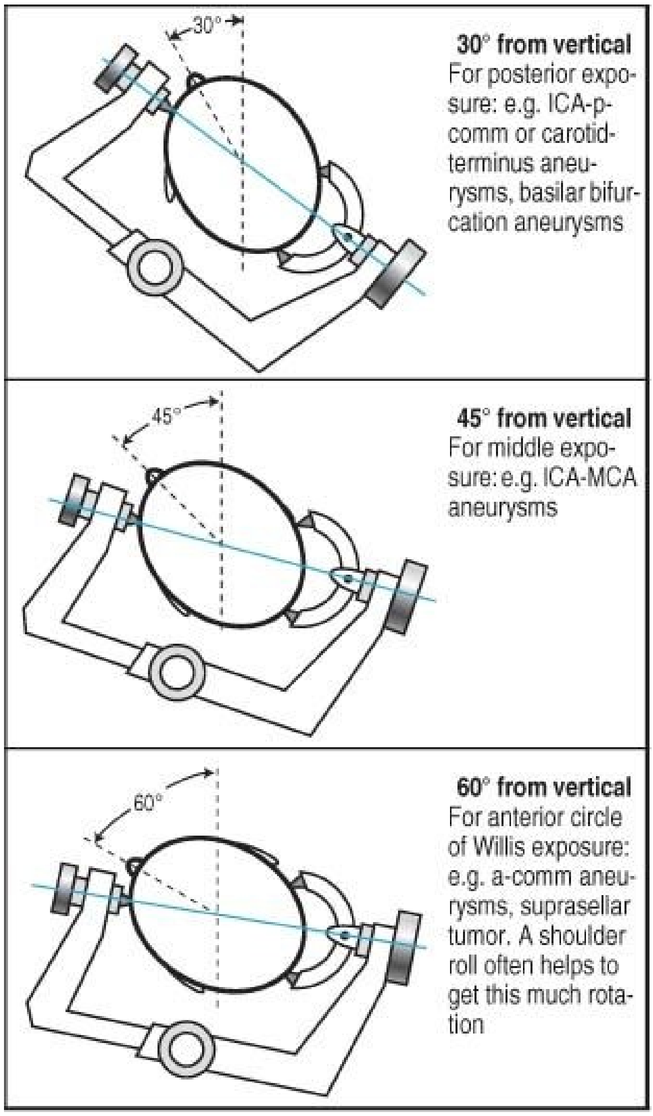

Figure 7-7 Head position for pterional craniotomy depending on exposure required. The blue line indicates the approximate centerline

ROOM ARRANGEMENT

1. microscope: observer tube to operator's right for either right or left pterional crani

SKIN INCISION

See Figure 7-8. From zygomatic arch 1 cm in front of tragus (to avoid frontalis branch of facial nerve and frontal branch of superficial temporal artery), curving slightly anteriorly, staying behind hairline to widow's peak, optional additional curve beyond midline to aid in skin retraction. Over temporalis muscle, incise skin down to but not through temporalis fascia.

The temporalis muscle may be incised caudal to the skin incision (i.e. closer to zygomatic arch): this minimizes the muscle mass that needs to be retracted inferiorly and yet keeps the scar behind hairline (note: there is an increased risk of frontalis weakness with this technique than if the temporalis muscle is incised inline with the skin incision).

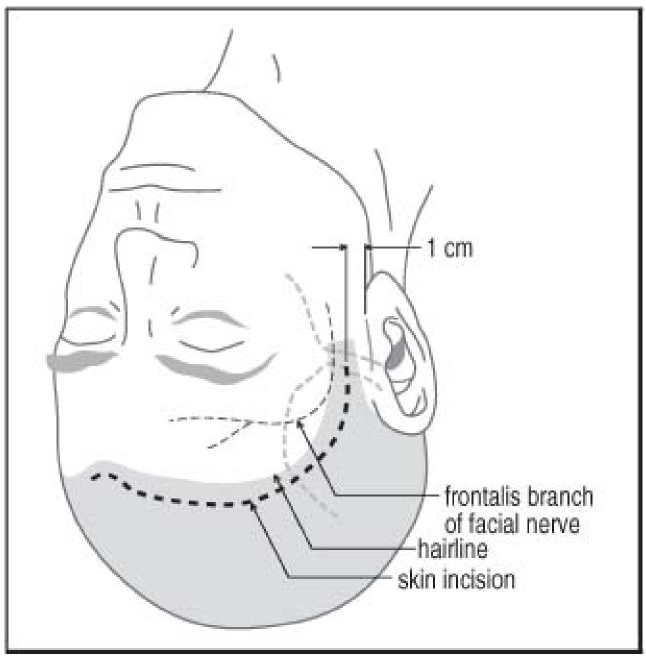

Figure 7-8 Skin incision for pterional craniotomy

CRANIOTOMY

There are numerous ways to cross the pterion (the lesser wing of the sphenoid makes this difficult). One method is outlined here, *see Figure 7-9*.

Burr holes

Two burr holes are sufficient; made as far caudally as possible to minimize the amount of bone to be rongeured off to gain access to the floor of the middle cranial fossa. One burr hole is made at the posterior insertion of the zygomatic arch ("**A**" in *Figure 7-9*); this burr hole may be placed slightly forward when

exposure is centered over structures around the ACoA (e.g. suprasellar tumor). The second burr hole ("**Z**") is made at the intersection of the zygomatic bone (near the frontozygomatic suture), the superior temporal line and the supraorbital ridge. The hole should be as low as possible on the orbit (Yasargil facetiously said "If you don't see intraorbital fat, you're not low enough."), aim the drill slightly superiorly to avoid actually entering the orbit. The dura is dissected off the inner table with a Penfield #3 dissector.

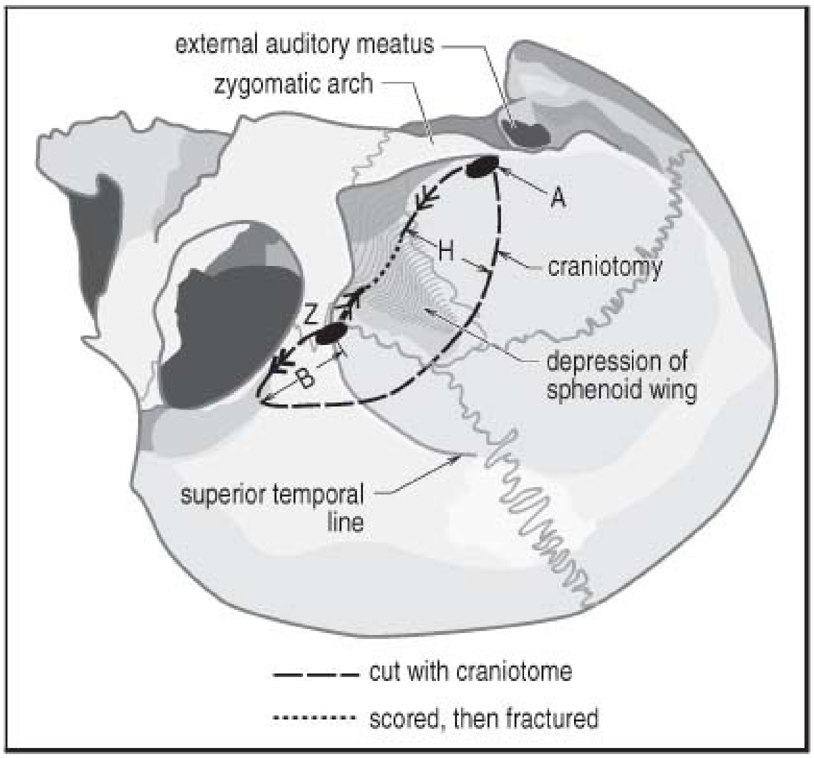

Figure 7-9 Skull landmarks for right pterional craniotomy

Craniotomy

The resulting bone flap is centered over the depression of the sphenoid ridge. Approximately 33% of the craniotomy is anterior to the anterior margin of temporalis muscle insertion, ≈ 66% is posterior.

With the craniotome, starting at the frontal burr hole the craniotomy is taken anteriorly across the anterior margin of the superior temporal line staying as low as possible on the orbit (to obviate having to rongeur bone, which is unsightly on the forehead). The distance "**B**" from the medial extent of the craniotomy to the frontal burr hole is 3 cm for anterior circulation aneurysms. For the approaches to skull base (e.g. Dolenc approach), distance "B" is larger and takes the opening to ≈ the mid orbit. Then from point "B", a sharp superior turn is made and the

opening is taken back to point “A”. The height (“**H**”) of the craniotomy needs to be only ≈ 3 cm for aneurysms of the Circle of Willis, and slightly larger (≈ 5 cm) for middle cerebral artery aneurysms. Minimal exposure of temporal cortex is necessary for aneurysms of the skull base region. For large flaps (e.g. for tumors), “H” is made larger to expose more temporal lobe.

From the frontal burr hole, the craniotomy is then taken posteriorly towards the depression corresponding to the sphenoid wing until the drill hangs up.

The craniotomy from the posterior burr hole is taken forward towards the depression corresponding to the sphenoid wing until the drill hangs up.

The bone between the two points where the drill hangs up is scored with the craniotome, and then the bone is fractured at this point. A rongeur is used to remove as much sphenoid wing as possible.

Dural flap

Curvilinear, centered over sphenoid wing, retracted inferiorly with dural stitch.

Dissection

For some anterior circulation aneurysms (e.g. MCA aneurysms) and for the Yasargil approach to basilar tip aneurysms, the sylvian fissure needs to be split. This can be accomplished by working from the lateral aspect of the fissure medially, or, by starting at the point where the carotid artery penetrates the fissure and working laterally. The latter method may be easier when prolific veins overly the junction of the frontal and temporal lobe. There are no arteries that cross the sylvian fissure, and so if the correct plane is maintained, no arteries need to be sacrificed.

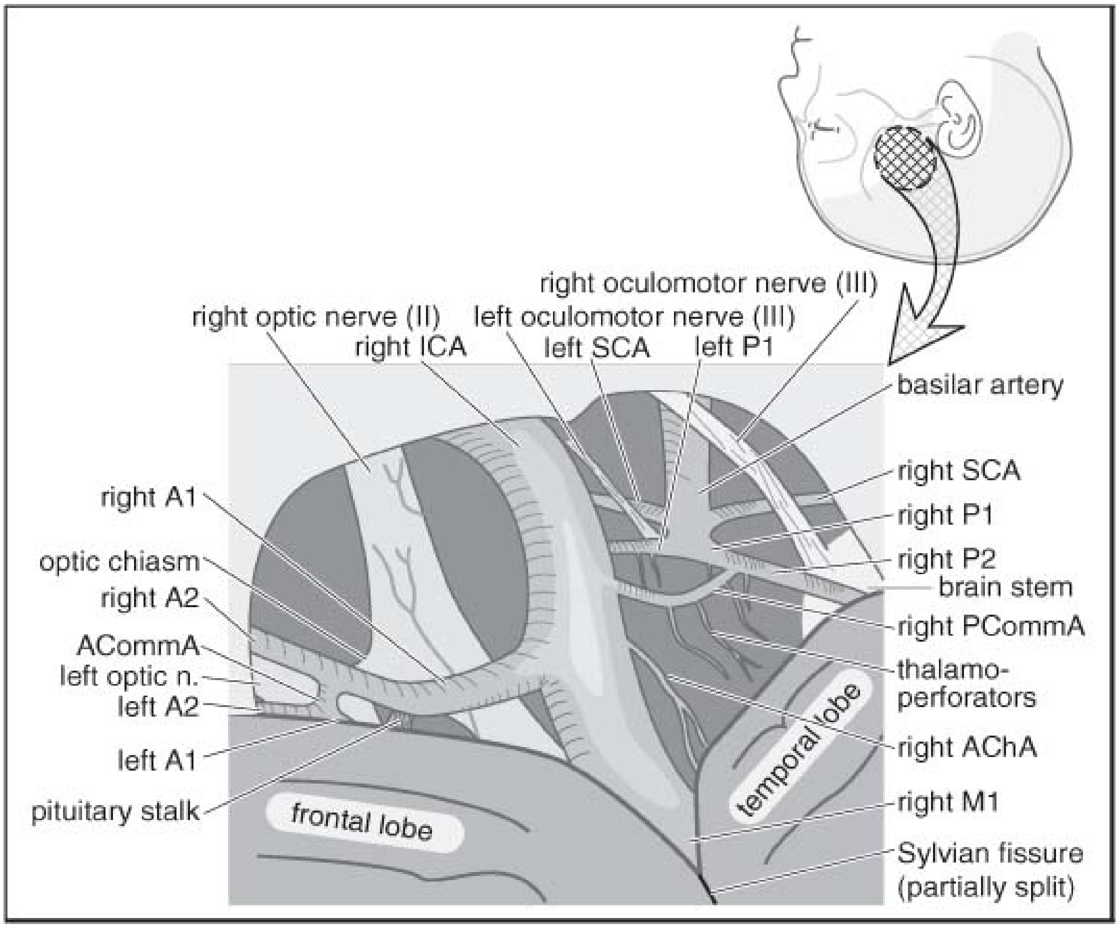

Figure 7-10 Right sided sylvian fissure dissection, surgical view

Figure 7-10 shows a theoretical exposure of the circle of Willis possible through a pterional craniotomy. This diagram is semi-schematic, and in reality dissection would be directed either anteriorly (e.g. to expose ACoA) or posteriorly (e.g. for basilar tip aneurysms) but not both.

7.4.7. Temporal craniotomy

INDICATIONS

1. temporal lobe biopsy: herpes simplex encephalitis
2. temporal lobectomy: for resection of seizure focus, decompression post-trauma…
3. hematoma (epidural or subdural) overlying temporal lobe
4. tumors of the temporal lobe
5. small, laterally located vestibular schwannomas[47]

6. access to the floor of the middle cranial fossa (including foramen ovale/Meckel's cave, the labyrinthine and upper tympanic portion of the facial nerve)
7. access to **medial temporal lobe** e.g. for amygdalo-hippocampectomy (*see page 423*) or for mesial temporal sclerosis (*see page 395*)

TECHNIQUE

Two basic methods for temporal craniotomy:

1. small craniotomy or craniectomy through a linear skin incision: good for cortical biopsy or draining chronic subdural hematoma. Also permits access to floor of middle fossa. Simple quick closure
2. question-mark skin incision with standard craniotomy flap: useful for temporal lobe exposure for tumor or acute hematoma

POSITION

- patient supine with shoulder roll (to assist in rotating neck to get head almost horizontal)
- elevate thorax 10-15°: reduces venous distension
- flex knees slightly
- Mayfield 3 pin head-holder: true AP with single pin anteriorly
- head rotated almost horizontal to floor: avoid over-extending to prevent kinking neck veins

SMALL CRANIECTOMY

Linear skin incision completely within the extent of the temporalis muscle. To access the temporal tip: place the incision midway between the lateral canthus and external auditory canal **(EAC)**; extend it from the zygomatic arch upward for ≈ 6 cm. For small, laterally located vestibular schwannomas, the incision is made 0.5 cm anterior to the EAC extending ≈ 7-8 cm above the zygomatic arch[47]. To drain a subdural, place the incision just anterior to the tragus and start it 1-2 cm above the zygomatic arch for ≈ 6 cm (modified based on the location of the epicenter of the subdural). Take the incision down to temporalis fascia with the knife, and incise the fascia and muscle with Bovie cautery. Spread with self-retaining retractors, and make a burr hole. Enlarge with rongeurs and/or Kerrison punches.

STANDARD CRANIOTOMY

Question-mark skin incision

See *Figure 7-11*. Used for access to the temporal lobe including tip (a *reverse* question mark incision may be used to gain access to the middle and posterior temporal lobe).

- the pinna is either sutured inferiorly out of the way before draping, or it can be folded under the drapes which may be stapled to the skin
- the lower limb extends from the zygomatic arch just anterior to the tragus (to avoid the superficial temporal artery)
- at the level of the top of the pinna it curves as far posteriorly as ≈ 6-7 cm on the non-dominant side, or ≈ 8-9 cm on the dominant side (these dimensions allow access to the "safe" area of temporal tip for lobectomy)
- then superiorly to the level of the superior temporal line
- then anteriorly towards the forehead, stopping at the hair line

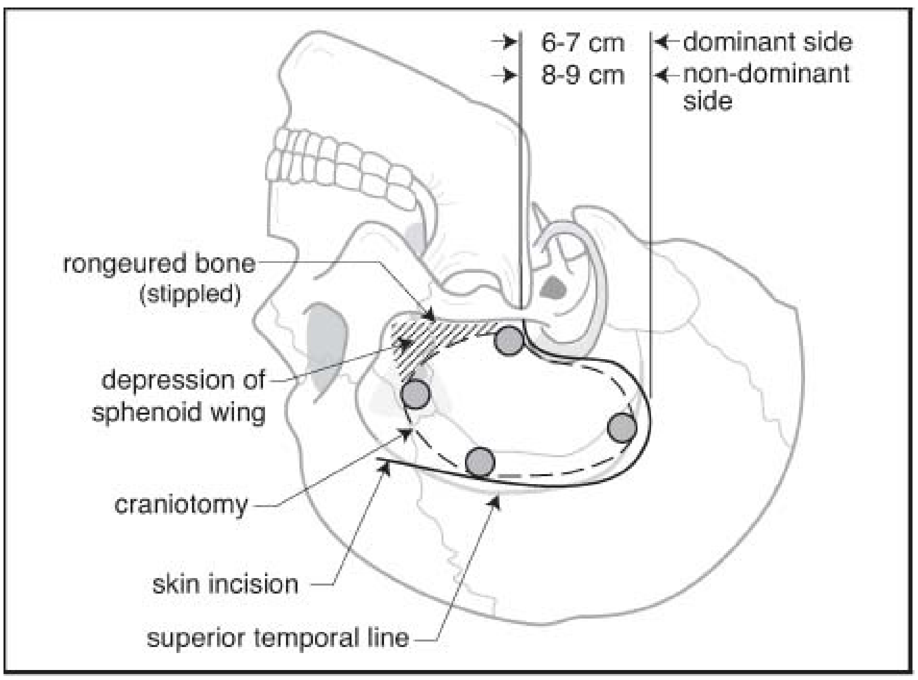

Figure 7-11 Temporal craniotomy (exposing entire temporal lobe)

Burr hole placement

1. at the posterior insertion of the zygomatic arch
2. at upper anterior junction of zygomatic arch
3. one or two burr holes along posterior and superior aspect of the skin incision

Craniotomy

Connect the burr holes with the craniotome, keeping as low as possible in the middle fossa to minimize the amount of bone that must be rongeured. The remaining bone is rongeured down to the floor of the middle fossa (cross-hatched area in *Figure 7-11*).

Temporal lobectomy

✖ Danger points:

1. dominant hemisphere: Wernicke's speech area. Although variable (see *Temporal lobectomy*, page 423), one can usually safely resect up to 4-5 cm from temporal tip
2. non-dominant hemisphere: one can resect up to 6-7 cm before running the risk of injuring the optic radiation
3. sylvian fissure (middle cerebral artery): it is best to amputate the temporal lobe backward from the tip for the extent of the desired resection, and then work deep
4. medially, the incisura should be identified to avoid injury to the brain stem which lies just medial to this

---

7.4.8. Frontal craniotomy

INDICATIONS

1. access to frontal lobe: e.g. for infiltrating tumor
2. approach to third ventricle or to sellar region tumors in some situations, including craniopharyngiomas, planum sphenoidale meningiomas
3. repair of ethmoidal CSF fistula

✖ **Danger points:**

1. anterior cerebral arteries in the midline (deep)
2. superior sagittal sinus **(SSS)** in the midline (note: the SSS may be sacrificed in its anterior third without engendering venous infarction in most cases, whereas venous infarction will almost always occur with division of the SSS posterior to that)
3. avoid inadvertently crossing the midline into the contralateral hemisphere through the corpus callosum
4. dominant hemisphere: Broca's (motor speech) area is located in the

inferior frontal gyrus

TECHNIQUE

Two basic choices for craniotomy:

1. unilateral craniotomy through a curved skin incision taken anteriorly up to the hairline: used when one does not need to be low in the frontal fossa in the midline (otherwise the skin incision would have to be taken far into forehead) and when there is no need to cross the midline
2. large bifrontal skin incision from "ear-to-ear" (souttar skin incision[48]) allowing low approach to one or both frontal fossa

UNILATERAL FRONTAL CRANIOTOMY

See Figure 7-12. Skin incision starts < 1 cm anterior to the tragus, and does not need to go all the way down to the zygomatic arch. It curves superiorly and slightly posteriorly before being taken to the midline frontally.

Burr holes

1. at the junction of the superior temporal line and the orbital rim
2. just posterior to the depression of the sphenoid wing (behind the pterion)
3. anteriorly just behind the hairline to avoid having a burr hole under the forehead (which causes an unsightly depression)
4. superiorly

BILATERAL FRONTAL CRANIOTOMY

1. "ear-to-ear" or souttar skin incision
   A. just behind hairline with a slight widow's peak at the front
   B. does not need to go all the way to the zygomatic arch, it just needs to be ≈ as low as the orbital roof
   C. unlike pterional craniotomy, usually do not need to incise the temporalis muscle and fascia. Dissect the flap off the muscle/fascia
   D. if a periosteal flap is likely to be needed, it sometimes helps not to incise the periosteum at the same time as the skin incision. Then, the periosteum can be incised *behind* the skin incision to yield a longer periosteal graft than would have otherwise been obtained
2. burr holes: to avoid burr hole defects on the forehead, the bone flap can be created with two burr holes straddling the superior sagittal sinus **(SSS)**

close to the skin incision, and two burr holes laterally

3. the SSS may be divided low, near the orbital roof, with little risk
4. if the frontal sinus is entered, it is dealt with as outlined under *Frontal sinus fractures*, *page 889*

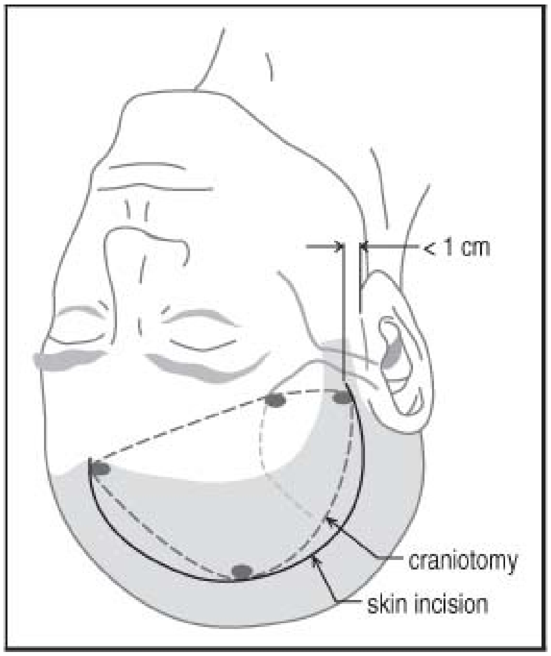

Figure 7-12 Unilateral frontal craniotomy

7.4.9. Occipital craniotomy

INDICATIONS

Occipital lobe tumors including posterior falx meningiomas or tentorial meningiomas with only supratentorial component. Occipital lobe intracerebral hemorrhages.

POSITIONS

Supine

Shoulder roll on affected side; elevate thorax 15°. Mayfield 3 pin headholder with single pin in forehead off to the side of the crani, double pin just over midline on opposite side.

Lateral oblique

- affected side up, can operate either
  - A. from behind patient similar to p-fossa crani for CPA lesion
  - OR
  - B. from top of table
- alternative approach: affected side down. Useful in lesions adjacent to the falx (see *Interhemispheric approach* above)

7.4.10. Decompressive craniectomy

Indications: controversial. Include:

1. malignant middle cerebral artery occlusion syndrome (*see page 1022*) primarily for nondominant hemisphere. Use on dominant side is more controversial
2. traumatic intracranial hypertension
   - A. as an adjunct for persistent intracranial hypertension when other ICP control measures fail[61] (*see page 892*)
   - B. early in the management: may be considered for patients undergoing emergent surgery (for fracture, EDH, SDH…)[62]
3. uncontrollable brain swelling during craniotomy (*see page 147*)
4. reported in children with refractory nontraumatic intracranial hypertension[63] (e.g. infection, infarction, Reye's syndrome…)

Potential complications:

1. bleeding
2. herniation of the brain through the opening, compressing and lacerating the brain on the bone edges (risk may be reduced by making generous craniectomy)
3. post-op injury to the brain from inadvertent external pressure applied to the now relatively less protected brain
4. post-op fluid collections: hygromas or hematomas at the operative site, on the contralateral side, or interhemispheric

TECHNIQUES

General considerations

1. it is necessary to open the dura
2. options for the removed bone flap
   A. discard it: this may be the best option when the bone flap has been contaminated as a result of an open traumatic scalp laceration
   B. place it in a separate subcutaneous pouch in the patient's abdomen for later retrieval and reimplantation into the skull. This is especially helpful if the patient's own skull is preferred and the patient does not live in the area where he/she is having the surgery
   C. store it for future implantation: saturate with sterile solution (e.g. RPMI medium 1640 www.invitrogen.com/GIBCO) and then place within sterile storage (e.g. intestinal bags which are then placed in a sterile plastic container) and store in a bone freezer at -80° C
   D. for non-contaminated situations (e.g. stroke): reimplantation can be considered after 6-12 weeks
3. bone openings need to be large (e.g. > 12 cm diameter[64], often > 15 cm)

POSTERIOR FOSSA DECOMPRESSIVE CRANIECTOMY

1. skin incision: midline skin incision from above inion to ≈ C2 spinous process
2. bone opening: laterally to sigmoid sinuses, superiorly to transverse sinus. C1 laminectomy is typically performed as well[63]
3. dural opening: "Y" shaped incision

HEMICRANIECTOMY

1. some prefer use of a Mayfield headholder placed low (*see Figure 7-13*) to give greater access[62] (not feasible with severe comminuted skull fractures)
2. AP axis of head is placed horizontal to floor (unless C-spine not cleared or if neck too immobile - one may compensate for this by rotating table)
3. skin incision: two options
   A. (*Figure 7-14-A*) starts at widow's peak, similar to trauma flap (*see page 865*), but with increased exposure by taking it posteriorly close to the inion then turning sharply anteriorly and hugging the ear to preserve blood supply
   B. (*Figure 7-14-B*) "T" incision. Less risk of flap ischemia. The "T" joins the midline incision behind the coronal suture to preserve the STA[62]

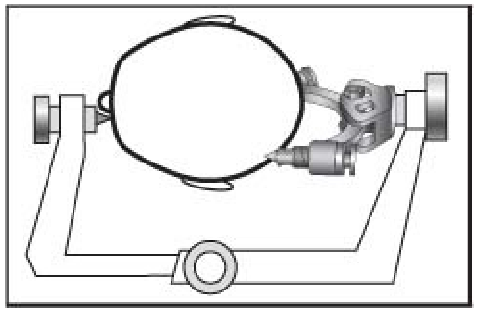

Figure 7-13 Position of head and head-holder for right hemicraniectomy (looking down on top of patient's head)

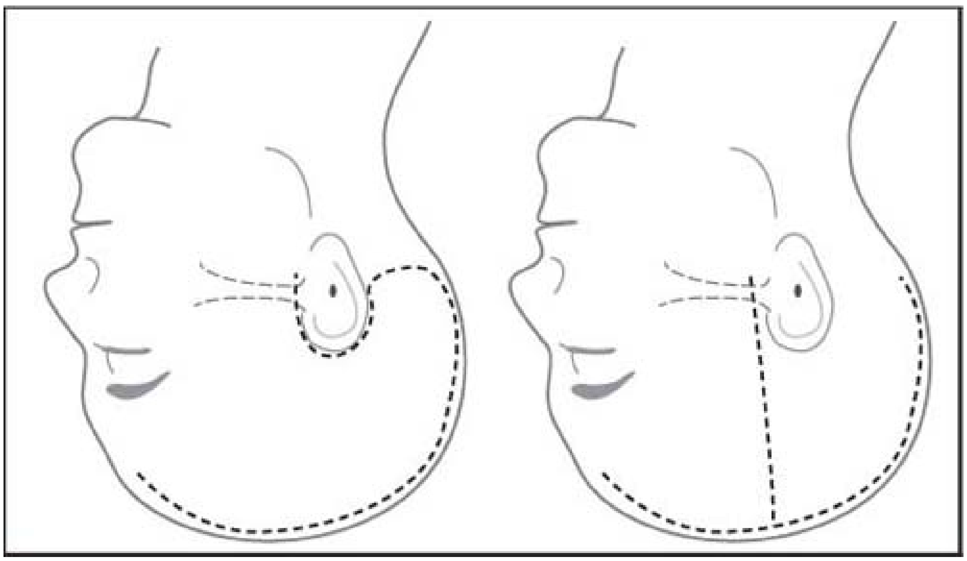

Figure 7-14 Two options for skin incision for hemicraniectomy (see text)

C. burr holes (*see Figure 7-15*): a burr hole is made just above the posterior root of the zygomatic arch, a second one may be made just behind the frontal insertion of the zygomatic arch, inferior to the superior temporal line

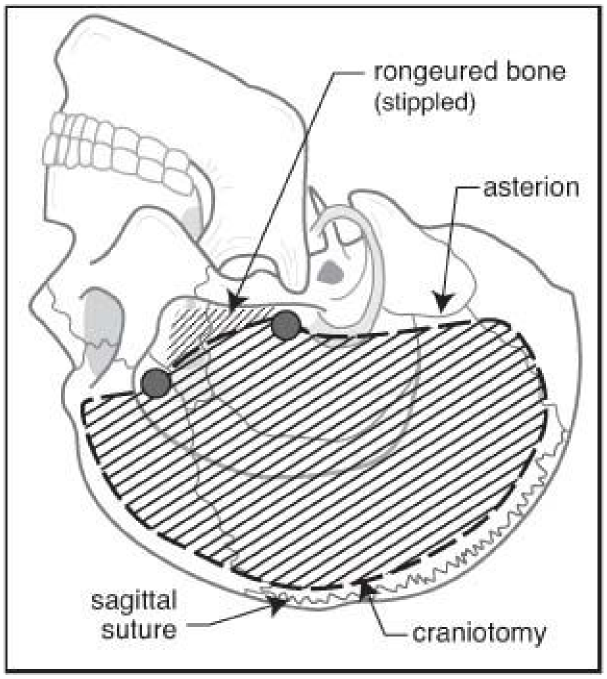

Figure 7-15 Hemicraniectomy bone flap

D. bone flap: proceed posteriorly from the posterior zygomatic arch using the footplated craniotome. Posteriorly, stay ≈ 1 cm superior to asterion to avoid the transverse sinus. The flap is taken 1 cm beyond the lambdoid suture, and then up towards the sagittal suture, crossing the lambdoid suture again (this leaves a small amount of bone posteriorly on which the head can rest post-op). An anterior turn is made 1 cm short of the sagittal suture to avoid the superior sagittal sinus, and the sagittal suture is paralleled. The coronal suture is crossed and the drill is taken as low as possible in the frontal fossa near the midline. Staying as low as possible, the orbital roof is followed posteriorly towards the second burr hole. The burr holes are then connected

E. some bone may need to be rongeured to expose the floor of the middle fossa (stippled area in *Figure 7-15*)

F. dural opening: based inferiorly, taken to 1 cm short of the craniotomy edge. Dural releasing incisions may be made at intervals up to the bone margin to avoid strangulation of the brain on the dural edge

G. duroplasy
   1. onlay: 2 cm wide strips of dural substitute can then be placed partway under the dural edge around the periphery to isolate the brain from the undersurface of the skin flap where there will be a

gap in the dura

2. some authors suture a dural draft in place

H. the dural flap is then replaced on top of the brain and dural substitute strips, and is not sutured

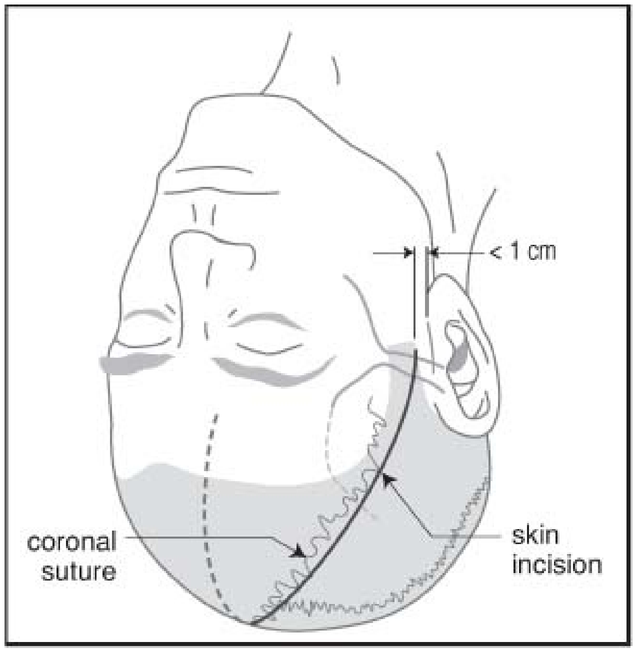

Figure 7-16 Bilateral craniectomy skin incision

Bilateral craniectomy

The above procedure can be performed bilaterally, however, it is difficult to position the head to do this. Alternatively, a bifrontal craniectomy can be performed.

1. skin incision: bicoronal, posterior to the coronal suture (*see Figure 7-16*)
2. burr holes: may use the same ones as for hemicraniectomy (*see above*) bilaterally. Addition burr holes to straddle the superior sagittal sinus may be made if a large single bone flap is planned
3. bone flap: two options, both are taken back to the coronal suture
   A. a single large bone flap[65] extending back to the coronal sutures, or
   B. two frontal flaps leaving a thin strip of bone in the midline overlying the superior sagittal sinus (if this strip is too wide, it can damage the brain)

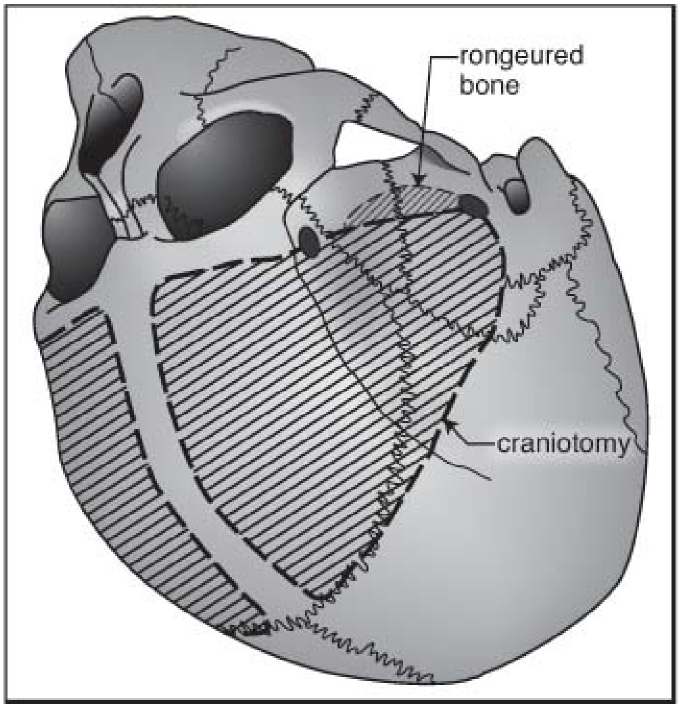

Figure 7-17 Bilateral craniectomy skull flap Shown with 2 separate frontal flaps (the preserved midline bone strip over the superior sagittal sinus is optional)

4. dural opening: bilateral, based against the midline (superior sagittal sinus)

7.4.11. Approaches to the lateral ventricle

Classic review[40] (p 561-74) summarized:

1. atrium (AKA trigone)[50]; numerous approaches include:
   A. middle temporal gyrus: through the dilated temporal horn
   B. lateral temporal parietal
   C. superior parietal occipital
   D. transcallosal (*see below*)
   E. transtemporal horn: access to temporal horn is via lobectomy of the temporal tip
   F. occipital lobe incision or occipital lobectomy: recommended only if patient has homonymous hemianopsia pre-op
2. frontal horn
   A. middle frontal gyrus
3. midventricular body
   A. transcallosal

B. middle frontal gyrus: usually prevents access to vascular supply until most of the tumor is removed (especially for tumors supplied primarily by posterior choroidal artery)
4. temporal horn
A. middle temporal gyrus
B. transtemporal horn

7.4.12. Approaches to the third ventricle

Classic references review the microsurgical anatomy[51] and surgical approaches[52], and are briefly summarized below.

Alternative approaches for lesions of the anterior third ventricle[53]:

1. transcortical: approach is through the lateral ventricle and is feasible only in the presence of hydrocephalus; especially useful if the tumor extends from the third ventricle into one of the lateral ventricles. Risk of seizures is 5% (higher then with transcallosal). *See page 172*
2. transcallosal: may be preferable in the absence of hydrocephalus (*see below*)
   A. anterior transcallosal: good visualization of both walls of third ventricle; risk of bilateral forniceal damage
   B. posterior transcallosal: allows approach to quadrigeminal plate or pineal region; risk of damage to deep veins
3. subfrontal: allows four different approaches
   A. subchiasmatic: between optic nerve and optic chiasm
   B. optico-carotid: through the triangular space bordered by optic nerve medially, carotid artery laterally, and ACA posteriorly
   C. lamina terminalis: above the optic chiasm[54]
   D. transsphenoidal: requires removal of tuberculum sellae, planum sphenoi-dale, and anterior wall of the sella turcica
4. transsphenoidal
5. subtemporal
6. stereotactic: may be useful for aspiration of colloid cysts (see *Stereotactic drainage of colloid cysts*, page 666)

GENERAL PRINCIPLES OF TUMOR REMOVAL

Summarized[52]. During the approach, deep veins should be preserved at all

costs, even if it means stretching them to the point that they may rupture.

It is helpful to place a suture through the tumor capsule to act as a tether.

The tumor should first be removed from within the capsule; techniques include aspiration, and then opening the capsule and debulking from within. The capsule may then be collapsed and dissected from adherent structures. If the capsule adhesions seem unyielding, the most likely cause is incomplete intracapsular evacuation.

Vessels on the surface of the tumor should be presumed to be supplying normal brain, and should be dissected off the capsule once it is completely emptied.

TRANSCALLOSAL APPROACH TO LATERAL OR THIRD VENTRICLE

Performed through an interhemispheric approach to the corpus callosum **(CC)** via a parietal craniotomy, usually right sided in a left-hemisphere dominant patient.

INDICATIONS

Primarily for tumors or lesions of the lateral or third ventricle, including:

1. colloid cysts
2. craniopharyngiomas
3. cysticercosis cysts
4. thalamic glioma
5. AVM

BOOKING THE CASE - TRANSCALLOSAL SURGERY

Also see defaults & disclaimers (*page v*).

1. position: supine with pin headholder
2. equipment:
    A. microscope
    B. image guided navigation system
3. post op: ICU
4. consent (in lay terms for the patient - not all-inclusive):
    A. procedure: operation between the two halves of the brain to remove

lesion

B. alternatives: non-surgical management, surgery through the surface of the brain (transcortical), radiation therapy for some diagnoses

C. complications: stroke, "disconnection syndrome" (uncommon - *see page 423*), hydrocephalus with possible need for a shunt, memory deficits

TECHNIQUE[51, 52, 55]

See Figure 7-18. Image-guided navigation is very helpful in ascertaining the correct trajectory which permits minimizing the size of the callosotomy, and helps distinguish the corpus callosum from the cingulate gyri.

POSITION

Supine with neck flexed. Thorax elevated 20°. Spinal drain not used. Keep the head perfectly vertical to minimize disorientation that can easily occur with this approach. Alternatively, gravity retraction may be employed either by tilting the head slightly to the right (causing the right hemisphere to fall away) or by using the lateral position.

SKIN INCISION

Either of the following may be used:

1. inverted "U" with the top just left of midline, extending from **6 cm anterior** to the coronal suture to **2 cm behind** the coronal suture, taking the sides for 7-8 cm
2. souttar skin incision

CRANIOTOMY

Pre-op angiography is recommended to plan the position of the flap to avoid sacrificing large cortical veins. MRI may also suffice for this[56]. The bone flap is either trapezoidal or triangular in shape, for adequate exposure it is critical to go all the way to the superior sagittal sinus **(SSS)**. Several techniques may be used (NB: the SSS is often to the right of the sagittal suture - *see page 87*):

1. to expose the SSS, straddle the SSS with paired burr holes anteriorly and posteriorly, dissect the dura from the inner table between pairs, and make the longitudinal cut on the left of midline. Disadvantage: removing the midline bone puts the SSS at greater risk of injury and makes it more difficult to control lacerations

2. one can make the long cut well to the right of midline, and then under direct vision rongeur off the bone to the SSS. Safe, but leaves a large bone gap that may need to be filled (e.g. with methyl methacrylate) and is time consuming
3. most risky for causing a sagittal sinus laceration is to make the long cut just right of the midline (over the edge of the SSS, which may lacerate it)

To stay away from the motor strip and to keep the sagittal sinus exposure as anterior as possible, 2/3 of the opening should lie anterior to coronal suture, 1/3 posterior (generally: 6 cm total with 4 cm anterior and 2 cm posterior). The craniotomy extends laterally to 3-4 cm to right of mid-line. The last cut with the craniotome should connect the burr holes along the sinus (mid-line); leaving this cut for last permits rapid access to the sinus in case it is torn. The dural flap is based to-wards the sagittal sinus.

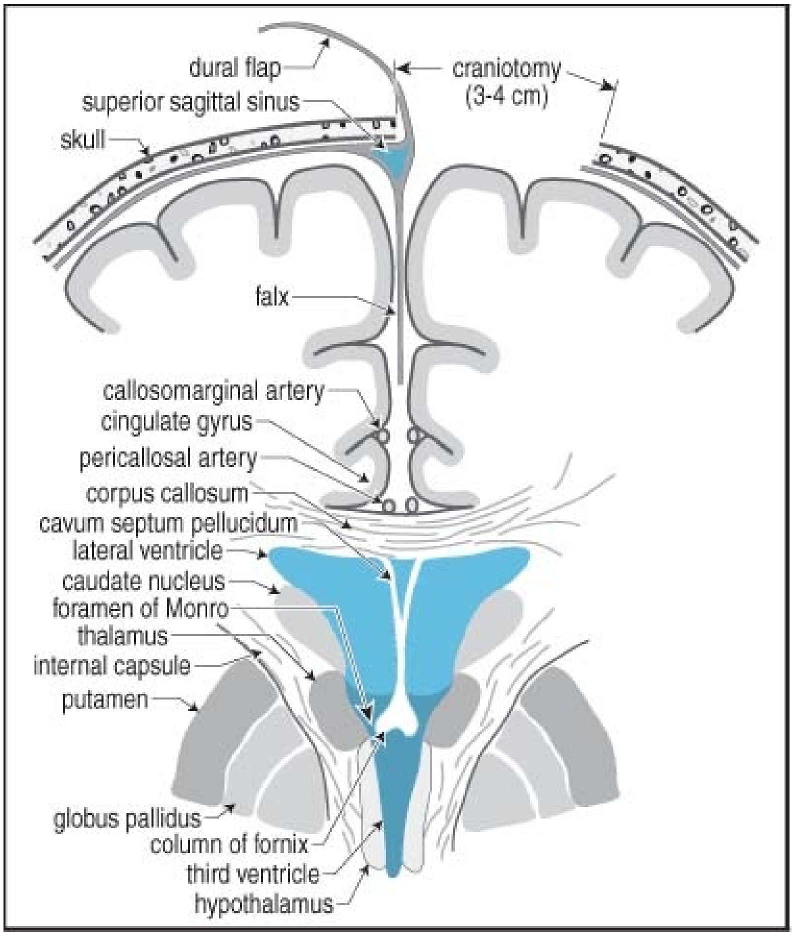

Figure 7-18 Transcallosal approach to the third ventricle: frontal view

APPROACH TO CORPUS CALLOSUM

None, or at most, only one bridging vein from the cortex to the sagittal sinus may be sacrificed (and then, only if it is not a large draining vein). Gently retract the right hemisphere. Avoid retractors on the sagittal sinus to prevent injury to

the SSS which may lead to sinus thrombosis (once CSF is released (with the callosotomy) retraction will be easier). Enter the interhemispheric fissure and follow the falx deep. Open the arachnoid membrane beyond the deep edge of the falx.

The two cingulate gyri may be adherent in the midline, and can easily be mistaken for the corpus callosum **(CC)**. This error may be compounded by mistaking the calloso-marginal arteries for the pericallosal arteries. Erroneously entering the cingulate gyrus disorients the surgeon and could cause injury to the pericallosal arteries. To differentiate: the CC is a pure white structure, is usually deeper than one anticipates, and is appreciated beneath the paired pericallosal arteries. Image guided surgery or measuring the depth to the CC on the pre-op MRI may help.

Callosotomy

The callosotomy is usually performed between the two pericallosal arteries. Some arterial branches may cross the midline, occasionally it is necessary to sacrifice some. **Trajectory**: a line drawn from the coronal suture (in the midline) to the external auditory canal (the foramen of Monro lies along this line); this helps avoid the tendency to tunnel posteriorly through the CC. Either the bipolar cautery, suction and sharp knife, or the laser is used to make the callosotomy. In hydrocephalus, the callosum will be thin. Entering the lateral ventricle releases CSF which aids retraction. When the foramen of Monro is occluded (e.g. with colloid cyst), it helps to fenestrate the septum pellucidum to prevent it from bulging into the ventricle in which one is operating (otherwise, as CSF is aspirated from the ipsilateral lateral ventricle, it cannot escape from the other).

Disconnection syndrome (*see page 423*): more common with posterior callosotomy (near the splenium) where more visual information crosses. The risk is reduced by creating a callosotomy **< 2.5 cm** in length extending posteriorly from a point 1-2 cm behind the tip of the genu[57]. For an interfornicial approach, the callosotomy must be perfectly midline.

Approach to third ventricle

Usually, the callosotomy will not be exactly midline, and one of the lateral ventricles will be entered. Great care must be taken to correctly identify which lateral ventricle has been entered, another potentially disorienting pitfall. For orientation (*see Figure 7-19*), the choroid plexus passes forward in the choroidal fissure to the foramen of Monro (which is medial) where it converges with the thalamostriate vein approaching from a more lateral position in the groove

between the thalamus and caudate. The septal and caudate veins approach the foramen from anterior. With colloid cysts, the foramen of Monro may be hard to recognize initially as it will be plugged with the cyst which can resemble the ependymal lining of the ventricle, but on close inspection is usually slightly grayer (the choroid plexus enters the posterior aspect of the foramen).

Another possible pitfall upon incising the CC is entering a **cavum septum pellucidum** (*see page 1218*). The give-away here is that no landmarks will be visible.

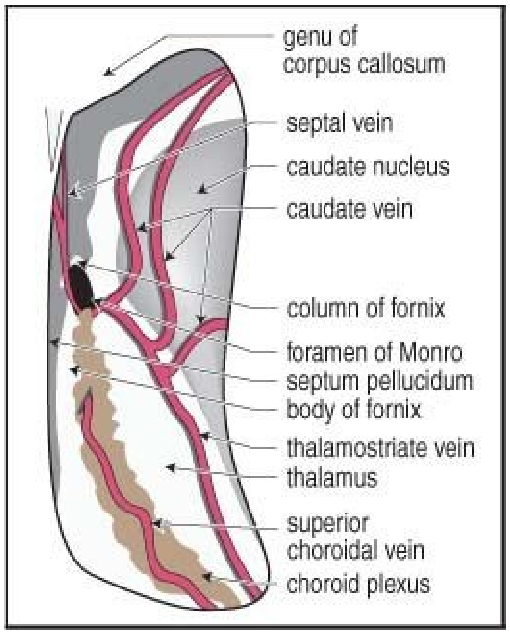

Figure 7-19 Right foramen of Monro viewed from above through right lateral ventricle (adapted[51])

Alternative approaches to third ventricle

1. interfornicial[57]: go above body of fornix, approaches roof of third ventricle. Well suited for lesions of the mid and posterior third ventricle. Callosotomy should be as close to midline as possible
2. from lateral ventricle through the foramen of Monro: with hydrocephalus, the foramen of Monro is usually dilated. If the foramen is too small for adequate access to the third ventricle, one can:
   A. return to the interfornicial approach (*see above*) or
   B. enlarge the foramen of Monro only if absolutely necessary. Either by:
      1. opening the foramen laterally
      2. the "subchoroidal" approach, making the incision posteriorly (sacrificing the thalamostriate vein) which is reportedly well

tolerated[52, 58]

3. last resort: incising the antero-superior margin of the foramen through the column of one fornix[57]. Caution: if the other fornix is non-functional for any reason, this would produce a bilateral forniceal lesion and may (but not definitely[57]) result in loss of short term memory and ability for new learning

Colloid cyst removal

It is critical to debulk and empty a cystic lesion, such as a colloid cyst, before delivering it from the third ventricle through the foramen of Monro. This will minimize the retraction and manipulation of the fornix. Inserting a needle and aspirating may work. The partially emptied cyst is grasped with a micro-pituitary and is delivered into the lateral ventricle through the foramen of Monro. One should only attempt to deliver the empty capsule through the foramen of Monro (see *General principles of tumor removal*, page 168). There is usually a stalk attaching the lesion to the roof of the third ventricle, this is coagulated with bipolar cautery and divided.

For other tumors, if the tumor is too large to fit through the foramen of Monro, it should be gutted from within.

Complications

1. venous infarction, may be due to:
   A. sacrifice of critical cortical draining veins: plan the flap to avoid this with preoperative angiography, or with sagittal T2WI MRI images[59]
   B. superior sagittal sinus **(SSS)** thrombosis[60]. Factors that may contribute to sinus injury include[56]:
      1. injury from retractor: avoid placing retractor on sinus (deformation of midline should not exceed 5 mm)
      2. over-retraction of the dural sinus flap or on SSS itself (lateral deformation should be < 2 cm)
      3. injury during the opening of the bone in the region of the sinus
      4. over-use of bipolar coagulation in the region of the SSS
      5. hypercoagulable state of the patient, including dehydration
2. transient mutism as a result of bilateral cingulate gyrus retraction or thalamic injury in conjunction with section of the midportion of the callosum[59]

TRANSCORTICAL APPROACH TO LATERAL OR THIRD VENTRICLE

INDICATIONS

In the absence of hydrocephalus, it is difficult to navigate through the ventricular system. Thus, with normal sized ventricles, the third ventricle and region of the foramen of Monro are better approached transcallosally (*see page 169*).

1. tumors of the atrium of the lateral ventricle
2. tumors of the roof of the third ventricle
3. third ventricular tumors with significant extension into one lateral ventricle

APPROACHES

1. posterior parietal
2. middle temporal gyrus: useful when temporal horn of lateral ventricle is dilated due to hydrocephalus caused by the tumor; access is through the temporal horn
3. **middle frontal gyrus approach**: a 4 cm incision is made parallel to the axis of the middle frontal gyrus, above and anterior to the expressive speech center (Broca's area) and anterior to the motor strip[52] (about the same point as used for frontal ventriculostomy, see *Kocher's point*,page 207)

7.4.13. Interhemispheric approach

INDICATIONS

For lesions abutting on midline, deep to surface, but superficial to corpus callosum (lesions that can "fall away" from midline). Similar to transcallosal approach above, except that the pathology can be placed on the down side, which allows gravity to retract the hemisphere and thus minimizes pressure necrosis injury from mechanical retractors.

TECHNIQUE

POSITION

True lateral (prevents getting lost from unusual angles). Head tilted slightly up.

Approach

Similar to transcallosal see *Position*, page 169. Need to be sure that lateral portion of craniotomy extends at least 4 cm from midline to minimize the necessity of retraction of brain against bone.

7.5. Cranioplasty

Indications

1. cosmetic restoration of external skull symmetry
2. relief of symptoms due to craniotomy defect (*see page 149*)
3. protection from trauma (blunt or penetrating) in area of post-craniotomy or post-traumatic skull defect

Timing

In certain cases, no consensus is possible. To avoid the risk of infection, authors recommend delaying cranioplasty with a “foreign body” at least 6 months after an open (i.e. contaminated) wound or one that traverses the nasal sinuses (*see page 887*). Others perform primary closure at the time of repair of the skull fracture. In “clean” cases (e.g. repair of defect after removing hemangioma of the skull) there is little argument against immediate cranioplasty.

Material

Options for material include:

1. the patients own bone if it was previously removed in a sterile fashion and saved either in a sterile manner under refrigeration, or in an abdominal pocket at the time of craniectomy
2. materials that can be formed by the surgeon
    A. methylmethacrylate: mixed in the O.R., molded to desired shape, and allowed to set before being attached to the skull usually with plates (alternatively, sutures or wire may be used). Setting is an exothermic reaction and ample irrigation and preferably removal from the operative site during the process avoids undesirable transmission of

heat to the brain

B. mesh: may be made of titanium or tantalum.

3. pre-fabricated custom flaps may be made by a number of commercial vendors using thin-cut CT scans to generate computer models of the defect and, if available, to use the contralateral side as a “mirror image” model for the desired shape

   A. methylmethacrylate

   B. PEEK (poly-ether-ether-ketone)

   C. titanium

4. split thickness calvaria

When foreign material is used, some recommend perforating the flap with a dozen or so drill holes to prevent the accumulation of fluid (either underneath the flap, or between the flap and the skull). This cannot be done with titanium plates.

7.6. Localizing levels in spine surgery

Identifying the correct level in spine surgery may be extremely challenging in certain situations. With the proliferation of minimally invasive spine techniques and the associated reduction in the structures that are directly visualized, the reliance on intraoperative imaging to determine the spinal level has increased. Gone are the days of “palpate the sacrum with your finger” through an open laminectomy wound.

Potential **pitfalls** which increase the chances of error, including:

1. pre-op, pathology is usually identified on MRI, and there are problems in translating MRI images to imaging available in the O.R.

   A. thoracic lesions: pre-op MRI usually counts from the top (C2) down, and in surgery it is often necessary to count from the bottom up, the count could be off if there are not 5 lumbar vertebra and 12 pairs of ribs

   B. lumbar spine: a well developed S1-2 disc (so-called lumbralized S1) or an L5 vertebra fused to the sacrum (sacralized L5) can confuse the count

2. not all patients have 12 ribs, or 5 “lumbar” vertebrae. In the modal (most common) human spine, there are 24 presacral vertebrae, however some

individuals have 23 and others have 25[A]. A HLD at the ultimate disc space (usually L5-S1) most often impinges on the 25th nerve root (however, in the variant cases, it may actually impinge on the 24th or 26th root)[66]

3. patients may have variant or ambiguous anatomy (e.g. a well-developed S1-2 disc space, an enlarged L1 transverse process which mimics a rib)
4. some "landmarks" used for localizing levels are unreliable or changeable
5. plain radiographs (and fluoroscopy) has difficult imaging the upper thoracic and sometimes the lower cervical spine
   A. on lateral imaging, the shoulder often obscure lower cervical/upper thoracic levels
   B. on AP imaging, the pronounced kyphosis of this region requires cranio-caudal angulation of the x-ray beam, which throws off imaging at other levels
6. spinous processes of lumbar and especially thoracic levels are below the corresponding VB
7. changes may occur between the time of the pre-op imaging and the surgery

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A. variations include: 11 or 13 rib bearing vertebrae, or a lumbosacral transitional vertebrae; the terminology of a "lumbralized S1 vertebrae" or a "sacralized L5 vertebrae" is imprecise and confusing

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Aids in determining spinal levels

1. image guided systems, when available
2. some O.R. suites have intra-op MRI or CT (or CT-like modalities, e.g. O-arm™ by Medtronic or ARCADIS® C-arm by Siemens) or image guided spine technology
3. ★ pre-op plain x-rays: lumbar (for lumbar pathology) and lumbar + thoracic (for thoracic pathology) to verify there are 12 thoracic vertebrae and 5 lumbar
4. on lateral lumbar spine x-rays, the top of the iliac crests are even with the L4 spinous process or the L4-5 interspinous space
5. on sagittal MRI there are generally no numbering cues, but on axial MRI, the sacral ala are reliably identifiable and this can be used to identify L5-S1 disc space
6. counting methods (if possible, using more than 1 method is highly recommended)

A. counting up from T12 or L5 on fluoro: be sure there are 12 ribs. You can "bridge" from lumbar or lower thoracic spine to higher thoracic levels using an instrument on the patient as a marker, or you can count up to one level (e.g. T9) and then while a hemostat is placed at this level on the fluoro screen, under real-time fluoro the machine is slowly moved up the spine and the hemostat is moved along with T9 (to count up from L5, verify there are 5 lumbar (i.e. non-rib bearing) presacral vertebrae). Radiation safety: avoid live fluoro as much as possible
B. AP view: starting at T12 (lowest rib) or from L5
C. lateral view: starting at the L5 and counting up
D. counting down from T1 (first rib) on AP fluoro: the fluoro machine may need to be angled caudally from the anterior position because of the thoracic kyphosis. Sometimes counting pedicles helps
E. by palpation: with thoracotomy, in the upper T-spine you can palpate the ribs from the inside from T1 and count down. The rib inserts at the upper end of the thoracic vertebra near the junction with the VB above (e.g. the T5 rib joins T5 close to the T4-5 disc space)

7.7. Anterior approaches to the spine

The following may be altered to take into account the possibility of overlap (e.g. a tumor of C7 which requires access down to at least T1 to permit stabilization).

Approaches

1. cervical spine
   A. anterior odontoid screw: *see page 181*
   B. C1-3 (upper cervical spine):
      1. transoral approach: including odontoidectomy (*see page 176*)
      2. extrapharyngeal approaches: use nasotracheal intubation (so that the mandible can be completely closed) through the contralateral nares. The head is slightly extended and is rotated 15° to the contralateral side. Avoid any oral tubes
         a. medial extrapharyngeal approach: medial to carotid sheath. Provides a more anterior position than the lateral retropharyn geal approach. Structures encountered: branches of external carotid artery, upper laryngeal nerves, hypoglossal nerve

b. lateral retropharyngeal approach: only the spinal accessory nerve is encountered

C. C3-C7: standard anterior cervical discectomy approach

2. thoracic spine
   A. T1 and below: extracavitary posterolateral approach. Bilateral costotransversectomies allows access to VB for resection of tumor, infection or fracture. Anterior cage placement can then be performed via this approach[67-71]
   B. T1-3: sternal splitting anterior approach (*see page 178*)
   C. T4-11:
      1. thoracotomy: in lateral decubitus position
         a. the patient needs to be able to tolerate deflation of the upper lung (sometimes partial deflation is adequate and is better tolerated)
         b. approach often by cardiovascular or thoracic surgeon. Left side is preferred by some (mobilizing the aorta is not difficult), others prefer right
         c. T3-4: often involves mobilizing some of the shoulder muscles which adds to complexity of exposure
         d. intubation: double-lumen tube permits unilateral lung deflation
      2. endoscopic approaches
   D. intra-op localization (determining level): especially challenging in the upper thoracic spine due to difficulty with lateral imaging through the shoulders. For pitfalls and compensatory measures *see page 173*
3. lumbar spine
   A. L1-5
      1. indications: tumor, fracture
      2. practical points
         a. aortic bifurcation located at the mid body of L3: a true anterior approach is therefore not practical. Therefore a <u>retroperitoneal approach</u> is used
         b. iliac crests may prevent a pure lateral approach to L4 and especially L5, which limits the placement of screws for the compression plate
         c. if a 360° fusion with pedicle screws is to be employed: potential problem with screws from compression plate hitting pedicle screws. There is some leeway in angulation of the pedicle screws to compensate for this
         d. complications to avoid:

i. injury to great vessels, especially the left iliac vein
ii. unnecessary sacrifice of intercoastal nerve which can cause atrophy of the abdominal muscles and eventration of the abdominal wall (not a true incisional hernia)
iii. do not enter the peritoneum
iv. injury to the kidney and ureter
v. ✖ anterior instrumentation must be avoided to prevent delayed vascular injury from repeated pulsations

3. position
   a. left sided approach is preferred (i.e. right lateral decubitus position). Exceptions where a left sided approach is used:
      i. primarily right-sided pathology
      ii. CT or MRI shows there is not enough room because of the location of the aorta
   b. level of pathology is positioned over the break in table (to get the iliac crest out of the way during initial approach - remember to unbreak table before final instrumentation!). Key: shoulders and pelvis true vertical for x-ray localization
   c. axillary roll
   d. flex the upper thigh (to relax psoas muscle) & knee
   e. stabilized with bean bag (keep patient exposed from midline anterior to posterior) and wide adhesive tape over pads at shoulder and thigh (keep iliac crest exposed for donor bone)
   f. use a fluoro compatible table, or place patient on table reversed to permit access by C-arm
4. incision[72]
   a. to access L2 and below: oblique incision starting anteroinferiorly at the edge of the rectus muscle extending cephalad and posteriorly through the bed of the 12th rib, ending posteriorly at the vertebral musculature
   b. exposure of L1: e.g. for instrumentation, requires extending the incision cephalad through the bed of the 10th rib, and may require radical takedown of the diaphragm for full exposure
5. approach[72]
   a. the 12th rib can be divided or disarticulated posteriorly, and may be used as a source of bone for fusion
   b. the kidney and ureter are retracted anteriorly, the psoas muscle is retracted laterally

c. segmental vessels are ligated or coagulated at the midportion of the VB
d. Bookwalter retractor is useful
6. surgical aspects
   a. to get the lateral compression plate true lateral, place it as "posterior" as possible (also keeps it away from the great vessels)
7. post op
   a. TLSO for 3 months
   b. increase activity slowly in brace
   c. some bulging of the flank muscles is normally associated with this approach

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7.7.1. Transoral approach to anterior craniocervical junction

Primarily useful for midline extradural lesions (approach to intradural lesions has been described[73], but the use has been extremely limited because of difficulties obtaining watertight closure and increased risk of meningitis). Refinements in techniques and equipment (e.g. flexible reinforced oral endotracheal tube, McGarver or Crockard retractor, operating microscope, and suturing transnasal red-rubber catheters to the uvula to aid in retraction) allows access from as high as the inferior third of the clivus to as low as C3 (and sometimes C4[74]) vertebral body without need for tracheostomy or splitting of the tongue. Additional access can be achieved with use of extended techniques including splitting of the hard & soft palate, tongue splitting, and transmandibular approach.

TRANSORAL ODONTOIDECTOMY

75% of patients undergoing transoral removal of the odontoid process required posterior fusion afterwards[75] due to ligamentous instability[76, 77].

Indications

Anterior extradural compression of the cervicomedullary junction as with pannus from rheumatoid arthritis, irreducible basilar invagination, tumors of C2, infection.

Stabilization

Most patients require surgical stabilization as a result of transoral odontoidectomy. While the stabilization intuitively seems like it should be done first, it is often done following the decompression at the same sitting or at a soon to follow date. Some reasons for decompressing before stabilization:

1. positioning the patient for fusion may cause neurologic compromise if there is cord compression
2. one can do a post-odontoidectomy MRI to determine if there is enough decompression. If not, a laminectomy can be done at the same time as the posterior stabilization
3. the amount of destabilization may not be known until after the odontoidectomy - in some cases a C1-2 fusion may suffice

Stabilization usually entails posterior occipitocervical fusion. Occasionally fusion may be limited to C1-2 or C1-3 without the occiput. It is also possible to place an anterior strut between the body of C2 and the clivus, or between C2 and C1. Fibula is recommended. Metal instrumentation should be avoided.

Pre-op preparation

1. make sure that the patient can open the mouth at least 25 mm. If not, then other approaches such as translabiomandibular should be considered
2. for conditions resulting in malalignment or basilar invagination, cervical traction for 1 or more days is sometimes required
3. radiographic evaluation
   A. cervical MRI without and with contrast to define the soft tissue pathology
   B. CT of the craniocervical junction with sagittal and coronal reconstruction
   C. CTA to assess the position and involvement of the vertebral arteries. Measuring the distance between the VAs provides useful information

Booking the case - transoral approach

Also see defaults & disclaimers (*page v*).

1. position: supine with pin headholder
2. equipment

   A. microscope
   B. high-speed drill with long bits
   C. C-arm
   D. image guided navigation system (if used)
3. instruments
   A. transoral set (usually includes oral retractor such as Crockard, Dingman, Dickman-Sonntag…)
   B. long instruments: microdiscectomy instruments often work
4. anesthesia: awake, fiberoptic endotracheal intubation
5. some surgeons use ENT to perform the approach and closure and for follow-up
6. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: transoral resection of odontoid, placement of halo-vest immobilization, MEP monitoring (MEP should be consented specifically due to risk of seizures). Need for posterior stabilization at the same setting or in the immediate future
   B. alternatives: nonsurgical management, radiation therapy for some diagnoses
   C. complications: CSF leak with possible meningitis, spinal cord injury, wound breakdown, swallowing difficulties (may require PEG tube), breathing problems (may require tracheostomy), seizures with MEP

Technical considerations

The surgical procedure is beyond the scope of this book. For details, see references[74, 75, 78]. Some key points:

Awake fiberoptic orotracheal intubation is employed. Nasotracheal **(NT)** is used by some, but at the narrow upper part of the exposure the NT tube tends to get in the way.

SSEP and MEP monitoring is used in appropriate cases.

Positioning: 3-point fixation with a Mayfield headholder is typically used. The patient is supine with no neck rotation (distorts the anatomical relationships and may bring one VA closer to the midline). Tilt the whole patient or the table towards the surgeon. 10-15° neck extension improves the exposure. Alternatively, the surgeon can stand above the patient who is kept perfectly supine.

A specialized retractor (e.g. Crockard transoral retractor) or a conventional Dingman retractor is placed. Check that the tongue is not being compressed

against the teeth.

Landmark: the tubercle of the atlas can be palpated through the posterior pharynx to locate the midline and for craniocaudal orientation.

The mucosa of the posterior pharynx is infiltrated with 1% lidocaine with epinephrine. Some authors culture the oropharynx to obtain drug sensitivities of organisms for use in the event of infection. Some advocate liberal topical use of 1% hydrocortisone ointment to the mucosa of the oropharynx and posterior tongue at the beginning and also during the operation to reduce intra-op and post-op swelling. Others feel it has no effect, and IV Decadron is used by some.

A 3 cm long vertical midline incision is made.

To reduce the risk of C1 spreading and allowing basilar invagination, C1 ring-sparing surgery may be attempted by removing only the inferior half to two-thirds of the anterior C1. When C1 ring-sparing is not done, the central 3 cm of the atlas is removed with a high-speed drill.

There is ≈ about 20-25 mm working distance between the two vertebral arteries at their point of closest approximation where they enter the foramen transversarium at the inferior aspect of the lateral mass of C2.

Closure: a two layer closure is preferred by some. Others recommend a single layer closure incorporating deep muscle, superficial muscle, and mucosa[74]. If the dura has been violated, a fascial patch is secured with tissue adhesive and a lumbar subarachnoid drain is placed in the O.R. and maintained at low pressure for 3-4 days. An NG tube is placed under direct visualization to avoid injury or penetration of the mucosal closure.

Possible complications

1. dural tear with CSF leak and risk of meningitis
2. vertebral artery injury
3. spinal cord injury

Post-op care

1. NG feeding or IV hyperalimentation is used initially (in anticipation of oropharyngeal swelling (lasts 2-3 days) and to avoid disruption of the mucosal closure)
2. intubation is maintained until the swelling subsides. Initial removal of the endotracheal tube over a tube changer facilitates reintubation if needed; the tube changer can be removed if no problem develops after 1 hour[78]
3. if the NG tube comes out, it should only be replaced under direct vision

(usually be ENT physician) to avoid injury/penetration of the mucosal incision
4. halo-vest immobilization is maintained until the posterior fusion is performed
5. for staged procedures when the fusion is being done at a later date, a post-op MRI should be done to assess the degree of decompression. If further decompression is needed, then a laminectomy can be added to the posterior fusion

Posterior stabilization

Transoral odontoidectomy produces instability in most cases (sometimes delayed)[76, 77].

For basilar invagination or occipitocervical instability, an occipitocervical fusion is recommended[78] (*see page 179*).

For C1-2 instability alone, a posterior C1-2 arthrodesis may be performed[78] (*see page 183*).

7.7.2. Anterior access to the cervico-thoracic junction/upper thoracic spine

Sternal splitting procedure

Permits access down to T3 (occasionally as far as T5) from an anterior midline approach (access to this region with a lateral (transthoracic) approach is poor due to small amount of room in pulmonary apices).

The neck and thorax are prepped down to the umbilicus. A hockey stick incision may be used, the horizontal portion is the usual for an ACF. The vertical limb is centered over the sternum. A CV surgeon splits the sternum and divides the sternocleidomastoid. This approach does not violate the pericardium or pleura, and a chest tube is not required (but is often used as a large bore drain to prevent hemomediastinum, and also as a precaution in case the parietal pleura is cut during the exposure). Because of the depth of the approach, longer instruments than the routine 7 inch length instruments used for an ACDF are required.

The exposed sternal edges may also be used to obtain cancellous bone for the graft.

7.7.3. Anterior access to mid & lower thoracic spine

Transthoracic approach

Position the patient on the O.R. on a bean-bag table with the break in the table under the level of pathology (remember to unbreak the table prior to instrumenting). Stabilize the patient using adhesive tape over surgical towels. An axillary roll is placed. A double-lumen endotracheal tube is used to permit dropping the lung on the side of the thoracotomy. If the patient does not tolerate completely deflating one lung, it is often adequate to just partially deflate the lung.

To increase the exposure, a rib may be resected. Generally, the level opened and the rib removed are one or two levels above the level of pathology (e.g. for T7 VB tumor, the T6 or T5 rib are removed).

If a compression plate is going to be used, the goal is to be lateral on the VB, to achieve this try to position it as far posterior as possible (rongeur off a little bit of the rib heads to facilitate this).

ANTERIOR ACCESS TO MID THORACIC SPINE

Laterality of approach: if the pathology does not dictate use of one side over another:

1. advantages of right-sided thoracotomy: the heart, mediastinum and brachiocephalic vein do not impede access
2. advantages of left-sided thoracotomy: aorta is easier to mobilize and retract

Determining the level in the upper T-spine can be quite difficult intraoperatively. Counting up from the sacrum on an AP view using live fluoro sometimes will work when lateral spine x-rays cannot penetrate the lower c-spine due to the shoulders.

ANTERIOR ACCESS TO LOWER THORACIC SPINE

Unless pathology is predominantly right-sided, a left-sided thoracotomy is preferred (easier to mobilize aorta than vena cava).

At about T10 and below, the attachment of the diaphragm increases the difficulty of the approach.

7.7.4. Anterior access to thoracolumbar junction

Retroperitoneal approach

Unless pathology is predominantly left-sided, a right-sided retroperitoneal approach is preferred (eliminates liver from impeding access).

7.7.5. Anterior access to the lumbar spine

Trans-abdominal approach

Through a Pfannenstiel's incision.

The location of the bifurcation of the inferior vena cava generally ranges from just above to just below the L4-5 disc space. When the bifurcation is at or below the disc space, procedures such as L4-5 ALIF van be very difficult if the veins cannot be mobilized off the vertebrae.

At L5-S1, the anterior sacral artery runs down the middle and has to be sacrificed to do an ALIF.

7.8. Surgical fusion of the cervical spine

Posterior cervical rigid fixation (lateral mass screws & rods, transarticular screws…) have largely supplanted non-rigid methods (wires/cables).

7.8.1. Occipitocervical fusion

The patient will lose about 30% of neck flexion mobility with this fusion.

Indications for occipitocervical fusion[79]:

1. traumatic occipitoatlantal dislocation
2. absence of a complete arch of C1
   A. congenital
   B. post-decompression[A]
   C. posttraumatic: "bursting" C1 fracture (bilateral or multiple C1 ring fractures)[A]. NB: some feel that this may be satisfactorily treated with

halo immobilization until the atlas fracture heals (as they almost all do) followed by C1 to C2 wiring/fusion[80]

3. congenital anomalies of the occipitocervical joints
4. upward migration of the odontoid into the foramen magnum
5. marked irreducible shifts of C1 or C2

A. alternatively, C1-2 lateral mass fusion (with or without lateral mass screws, *see page 184*) may be used in these cases if only the posterior arch of C1 is compromised

Disadvantages of occipitocervical fusion:

1. loss of movement at the occipitoatlantal junction further reduces the range of motion as follows[81]:
   A. flexion/extension: reduced by ≈ **30%** (13° occurs at occiput-C1 junction)
   B. lateral rotation: 10° is lost
   C. lateral bending: 8° is lost
2. non-union rate is higher than with C1-2 fusion alone[82]

Options

1. keel plate (placed centrally over the thickest portion of the occipital bone) connected via rods to cervical screws (C2 pedicle screws and C3 lateral mass screws): reduced range of motion (ROM) to 17% of normal in a cadaver study[83] (for technique, *see below*)
2. occipital condyle **(OC)**-C1 polyaxial screws[84]: *see below*
3. occipital-C1 (AKA atlantooccipital) transarticular screws (*see below*)
4. looped rod wired to the occiput via wire cables placed through holes drilled in the occiput. Reduced ROM only to 31% of normal[83]

KEEL PLATE OCCIPITAL-CERVICAL FUSION

Pre-op planning:

1. CT scan through C2
   A. to rule-out aberrant position of foramen transversarium
   B. to measure diameter of pedicles (may be best done on coronal sections due to the fact that the axial images are not usually oriented along path

of pedicle) and estimate length of screws to be used

C. to verify trajectory of screws

2. measure thickness of occipital bone to determine screw-length for occipital screws

Technique:

1. occipital keel screws/plate
   A. a drill, tap and screwdriver with flexible shafts or universal joints are usually needed because of interference from patient's skin
   B. midline holes are preferred since occipital bone is thickest here
   C. drill with drill guide to 8 mm, check depth with probe, if the inner cortex has not been breached, drill to 10 mm, check depth again, keep drilling 2 mm at a time until the inner cortex is breached, use that screw length
   D. SCREWS 4.5 diameter <u>blunt</u> screws, 8-12 mm length
2. C2 pedicle screws: see *C2 screws*, page 187
3. C3 lateral mass screws (if used): see *C3-6 fixation*, page 188

OCCIPITAL CONDYLE TO C1 POLYAXIAL SCREW FUSION[84, 85]

Utilizes polyaxial screws placed in the occipital condyles that are then connected to screws placed at lower levels (*see below*) via connecting rods.

1. PROS compared to occipital plate/keel instrumentation:
   A. circumvents problem of poor occipital bone purchase which may occur with keel plates
   B. can be used even following posterior fossa craniectomy
   C. greater surface area for fusion
   D. avoids risk of intracranial injury from occipital screws
2. CONS: due to condylar variability, not all patients are candidates
3. biomechanics: compared to occipital plate, similar stiffness in flexion-extension and axial rotation, increased stiffness to lateral bending[86]
4. clinical: 1 patient, 2 years F/U with solid OC fusion[87]

Pre-op planning: CT scan occiput through C2.

Technique:

Structures to avoid include: hypoglossal nerve in hypoglossal canal (just above the occipital condyles **(OC)**), carotid and vertebral arteries, jugular bulb. IG may be helpful

1. occipital condyle screws
    A. ENTRY 4-5 mm lateral to the foramen magnum, 1-2 mm rostral to the atlanto-occipital joint (do not need to or want to expose the entire condyle - there is an emissary vein laterally which is best left alone)
    B. TRAJ 12-22° medial (mean: 17°), 5° maximal superior angulation
    C. SCREWS 3.5 mm diameter polyaxial screws; bicortical purchase obtained using 20-24 mm length (mean: 22 mm)
2. condyle screws are connected with 3mm diameter rods to either:
    A. screws in C1 lateral mass and C2 pedicles (*see page 187*), or
    B. C1-2 transarticular screws (*see page 184*)

Occipital-C1 (AKA atlantooccipital) transarticular screws[88, 89]

Reduced ROM to 3% of normal[83]

1. PROS: no compromise of C1-2 joint
2. CONS: steep trajectory requires additional incision at level of C-T junction
3. ENTRY midpoint of posterior C1 lateral mass
4. TRAJ 10-20° medially, aiming cranially to TARGET middle of occipital condyle
5. SCREWS 28-32 mm cannulated lag screws
6. biomechanics: ≈ equal to occipital plate-C1 lateral mass fusion[90]
7. clinical data: 2 cases reported, 2 year F/U, co complication

Post-op

1. for severe C1 fractures, or those with impaired bone healing capacity (elderly or unreliable patients, smokers…) a halo-vest is recommended **x** 8-12 weeks
2. otherwise, if C1 is not badly damaged, a collar that limits flexion (e.g. Miami-J collar) suffices **x** 8-12 weeks

7.8.2. Anterior odontoid screw fixation

Introduction

50% of axial rotation of the head occurs at the C1-C2 complex. Treatment of

odontoid fractures by C1-2 fusion significantly reduces this mobility (although subaxial articulations will compensate to some degree over time). Odontoid screw fixation **(OSF)** attempts to treat odontoid fractures by restoring the structural integrity of the odontoid process (osteosynthesis) without sacrificing the normal mobility.

Stability of the C1-2 joint depends primarily on the integrity of the odontoid process and the atlantal transverse ligament (which is the most important structure holding the odontoid process in position against the anterior arch of C1 - *see page 92*).

Evaluation

A full set of C-spine x-rays is needed, including an open-mouth odontoid view. MRI is recommended to rule-out disruption of atlantal transverse ligament. Cervical axial CT with coronal and sagittal reconstructions are also recommended to demonstrate the orientation of the fracture path and to verify the integrity of the posterior elements.

Indications

Reducible odontoid Type II fracture (and Type III fractures where the fracture line is in the cephalad portion of the body of C2 in an elderly patient who may not fuse as well with immobilization as a younger patient[91]). The transverse ligament must be intact.

Contraindications

1. fractures of the C2 vertebral body (except cephalad Type III fracture)
2. disruption of atlantal transverse ligament: see *Transverse atlantal ligament i (TAL) injuries*, page 957. May be directly demonstrated on MRI. Indirect evidence: if the sum of the overhang of the lateral masses of C1 on C2 exceeds 7 mm (rule of Spence, *see page 957*)
3. large odontoid fracture gap
4. irreducible fracture
5. age of fracture: controversial. Fusion rates in fracture > 18 months old was 25%[92]. Fracture < 6 months old have ≈ 90% fusion rate[92]
6. patients with short, thick necks and/or barrel chest: makes it difficult to achieve the proper angle. May be circumvented by the instrumentation distributed by Richard-Nephew which utilize a cannulated flexible drill,

tap and screwdriver
7. pathologic odontoid fracture
8. fracture line in oblique orientation to frontal plane (shearing forces can cause malalignment during screw tightening)

Booking the case - odontoid screw fixation

See defaults & disclaimers (*page v*).

1. position: supine head on horseshoe headrest, halter traction
2. anesthesia: awake fiberoptic or nasotracheal intubation. Do NOT use a wire reinforced endotracheal tube
3. equipment: **2** C-arms for biplane fluoro, or O-arm image guidance
4. instrumentation:
   A. ACDF surgical set
   B. tube retractor (e.g. METRx® by Medtronic)
   C. some surgeons use specialized instrumentation (e.g. Apfelbaum set)
5. implants: cannulated screw set
6. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery to place screw(s) from the front of the neck across the fractured odontoid bone. Possible posterior approach in case the anterior approach cannot be completed
   B. alternatives: nonsurgical management in a collar, fusion
   C. complications: screw breakage/pullout, failure to fuse which might require addition surgery (which will reduce neck motion)

Technique summary

Various instrumentation systems have been developed to facilitate the procedure. The following describes some of the basic elements that are not specific to any one instrumentation (see reference by Apfelbaum[93] for details of his instrumentation distributed by Aesculap Instrument Corporation, South San Francisco, CA).

Two C-arm fluoroscopy machines are mandatory for biplane imaging (simultaneous AP and lateral views). Some surgeons prefer placing 2 screws if there is enough bone to accommodate them, however, this may also reduce the amount of bone surface that can heal and the fusion rate appears to be the

same[94].

Anesthetic considerations: The anesthesiologist is positioned at the foot of the table. Awake fiberoptic or nasotracheal intubation is recommended, especially for easily dislocatable fractures. Do NOT use a wire reinforced endotracheal tube since the wire interferes with the AP imaging.

Position: Supine. The neck is placed in extension (critical to performing the procedure) either with Holter traction and a small shoulder roll with the head on a doughnut (a strip of tape across the forehead stabilizes the head), or a radiolucent head holder may be used. Place the lateral fluoro unit first, then the AP unit slides into the "C" of the lateral unit. Lateral fluoroscopy is used to assess reduction of the fracture fragment, and the head is repositioned to try and achieve reduction. If there is retrolisthesis of the odontoid, the neck may need to be slightly less extended. A radiolucent mouth gag is placed to hold the mouth open for AP transoral imaging (a gauze roll works well). Abort the procedure if AP and lateral fluoroscopic views do not adequately image the odontoid.

Approach: A Cloward-type of horizontal skin incision at ≈ C5-6 (the entry site can be verified by placing a guidewire adjacent to the patients neck and taking a lateral fluoro) and approach identical to anterior cervical discectomy is used (all the way to exposing the longus coli muscles - *see page 463*). A Kittner is used to dissect superiorly anterior to the longus coli muscles in the loose areolar tissue up to C2. A self-retaining retractor (e.g. Caspar retractor - not *distractor*) with a superior retractor blade is attached (or a hand-held retractor, preferably radiolucent, may be used). Alternatively, a retractor tube system[95] (e.g. METRx® by Medtronic) may be used. The bovie is used to remove the soft tissue over the inferior front of C2.

Procedure: Localization: lateral fluoro is used to place the tip of an awl as far anteriorly as possible on the inferior endplate of C2 (*see Figure 7-20*) (a common error is to go too far back along the inferior margin of C2, then the guidewire end up towards the back of the dens). AP fluoro is used place the awl in the exact center of the C2 body in the lateral dimension. The awl is used to make a pilot hole at this location.

Guidewire placement, drilling, tapping and ultimately screw placement are performed while monitoring the progress on frequent fluoro images, aiming for the exact middle of the dens on AP fluoro, and aiming towards the apex of the odontoid fracture fragment (skimming just within the anterior part of the C2 vertebral body) on lateral fluoro.

Drilling is performed under fluoro all the way through the apical cortex of the dens to avoid cracking the dens with the screw (the area just distal to the apex of the dens is safe).

A titanium partially threaded (lag) screw is placed. If an appropriately sized lag screw is not available, one can overdrill the part of the path through the body of C2 up to the fracture. In this way, a fully threaded screws can be used which will slip through the overdrilled hole and still have a lag effect on the fracture fragment. If a second screw is used, it may be fully threaded. In chronic nonunion cases, prior to advancing the screw a bifaced curette may be inserted within the fracture space to freshen the fracture site. The screw(s) should be drawn up tightly to the inferior edge of C2. *Figure 7-20* shows the final position of an anterior odontoid screw.

At the end of the procedure confirm integrity of the transverse ligament by carefully flexing the neck under lateral fluoro.

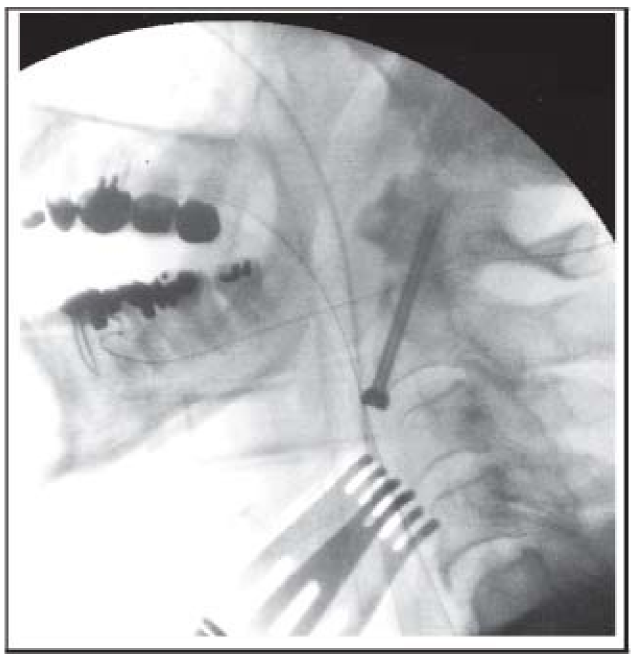

Figure 7-20 Final position of anterior odontoid screw

Postoperative immobilization: The immediate post-op strength of the odontoid + screw is only ≈ 50% of the normal odontoid. Therefore, a cervical brace is recommended for 6 weeks[91] (although some authors don't use one[93]). If the patient has significant osteoporosis, a halo brace is recommended.

Results: Healing takes ≈ 3 months (or longer with chronic nonunion). With fractures < 6 months old, the union rate was 95%. Chronic nonunions > 6

months old have a significant risk of hardware failure (screw breakage or pull-out), with a bony union rate of 31%, and 38% rate of presumed fibrous union[93]. Thus, in cases of chronic nonunion > 6 months old, C1-2 arthrodesis is probably a better choice unless the need to maintain motion is worth the risk of needing a second operation if this one fails.

The average technical complication rate is ≈ 6% (2% screw malposition, 1.5% screw breakout).

7.8.3. Atlantoaxial fusion (C1-2 arthrodesis)

The patient will lose about 50% of rotation of the head on the neck with this fusion.

INDICATIONS

1. instability of the C1-2 joints, including:
   A. atlantoaxial dislocation due to incompetence of the transverse atlantal ligament **(TAL)**:
      1. rheumatoid arthritis: symptomatic patients, or asymptomatic patients with subluxation ≥ 8 mm (*see page 496*)
      2. local infection
      3. trauma
      4. Down syndrome: due to laxity of the TAL (*see page 498*)
   B. incompetence of the odontoid process
      1. odontoid fractures meeting surgical criteria (*see page 964*), including
         a. Type II fractures with > 6 mm displacement
         b. instability at the fracture site in halo-vest traction
         c. chronic nonunion of odontoid fractures
         d. disruption of the transverse ligament
      2. following transoral odontoidectomy
      3. tumors destroying the odontoid process
2. vertebrobasilar insufficiency with head turning (bow hunter's sign): *see page 1159*

TECHNICAL CONSIDERATIONS

Come cases require incorporation of the occiput in addition to C1-2.

Surgical options include:

1. rigid instrumentation:
   A. C1-C2 fusion using polyaxial screws connected by rods:
      1. C1: screws placed in lateral masses. May be used in cases where the posterior arch of C1 is compromised
      2. C2 screw options:
         a. screws may be placed in pedicles (pars)
         b. screws may be placed in lateral masses
         c. crossed C2 laminar screws[96]
   B. C1-2 posterior transarticular facet screws **(TAS)**[97-99]
2. posterior cervical wiring and fusion: with the development of rigid fixation, these techniques have fallen by the wayside. While they are poor in limiting rotation, they are effective in limiting However, since the Dickman & Sonntag technique is effective in limiting extension, it has recently been used to offload C1 lateral mass screws which have a tendency to break at the point of entry to the bone
   A. interspinous fusion technique of Dickman and Sonntag: *see page 187*
   B. not presented here:
      1. Brooks fusion[100] (the Smith-Robinson technique as modified by Griswold[101]): C1 to C2 sublaminar wires with 2 wedge bone grafts
      2. Gallie fusion[40 (p 1477-93)] and its modifications: midline wire under the arch of C1 with an “H” bone graft
3. Halifax clamps with fusion[102]: these clamps are effective in minimizing movement in flexion, but are less stable in extension or with rotation
4. odontoid compression screw fixation: essentially only for odontoid Type II fractures < 6 months old with intact transverse ligament[103] (*see page 181*). Preserves more mobility than C1-2 fusion
5. combined anterolateral and posterior bone grafting[103]
6. combining anterior (transoral) decompression with posterior fusion: indicated when a significant anterior mass is present causing neural compression and/or making passage of sublaminar wires at C1 unsafe

7.8.3.1. Techniques of atlantoaxial fusion

Positioning

Patients are placed in a halo ring (with a gap in the back) and are then placed prone on the O.R. table on chest rolls. The halo ring is secured to the table using

a Mayfield adapter. The table will usually need to be positioned in a maximal reverse-Trendelenburg position to bring up the surgical area. The patient's feet are allowed to rest on a padded footplate on the table to prevent the patient from sliding down. Lateral intraoperative x-rays are taken after patient positioning.

Incision and approach

A midline skin incision is made from just below the inion to the spinous process of C5 or C6.

C1-2 TRANSARTICULAR FACET SCREWS (TAS)

May be used as an adjunct to posterior C1-2 wiring and bone graft (e.g. technique of Dickman and Sonntag, *see page 187*) to achieve immediate stabilization without the need for postoperative external orthosis, or in cases where the posterior arch of C1 is fractured or absent. ✖ A major risk of the procedure is vertebral artery **(VA)** injury. Therefore there is a growing interest in C1 lateral mass screws (*see page 185*).

Selection of candidates

May be appropriate in elderly patients or those with rheumatoid arthritis, in whom there may be slow fusion, or for those who have failed a previous attempt at C1-2 wiring/fusion. Also in young individuals who have ligamentous laxity.

All patients must have thin cut CT scans from the occipital condyles through C3 with sagittal reconstruction through the C1-2 facet on both sides to look for the presence of a vertebral artery in the intended path of the screw. Also, risk of VA injury can be reduced using CT scans reconstructed along the planned trajectory of the screw (aiming from a point 4 mm above the inferior C2 facet to a point in the anterior C1 button on CT[104]).

Technique summary

A number of instrumentation sets are available for the procedure, and each has its own nuances. The following is intended to primarily cover the basic procedure common to most or all (see reference by Apfelbaum[93] for details with that system).

Position:

Patient supine, with the head clamped in a Mayfield head-holder with a

slight military tuck of the chin. Lateral C-arm fluoroscopy is used for the procedure, and some have advocated biplane fluoro.

Approach:

Utilize a standard midline posterior laminectomy approach from occiput to the C3 spinous process. The lamina of C2 and the posterior arch of C1 are exposed to the lateral aspect of the C2 inferior articular facet. The lateral extent of the spinal canal is defined using a small angled curette. The C1-2 facet is curetted to facilitate arthrodesis and permits observation of the drill as it crosses the joint.

ENTRY 1-2 mm superior to the C2-3 facet on the midline axis of the pars interarticularis. The trajectory is determined fluoroscopically using a K-wire placed on the side of the neck as a guide, aiming it through the C2 inferior articular process, pars interarticularis, superior articular process and across the C1-2 articulation into the lateral mass of C1. This helps establish the appropriate entry site for the drill guide through a separate stab wound, usually around the T1-2 level, 2-3 cm off the midline.

TRAJ A pilot hole is then drilled using visual guidance to maintain a straight parasagittal course (it helps to stand on 1 or 2 footstools to eliminate some of the parallax error) and fluoroscopic guidance to maintain the trajectory towards the C1 lateral mass. An assistant can reduce any atlanto-axial translational malalignment using a towel clip on C1 or C2 just prior to the drill crossing the C1-2 facet joint. To minimize the risk of VA injury, keep the drill as far dorsally as possible within the pars interarticularis. The pilot hole is then tapped and a fully threaded titanium screw is placed. If brisk arterial bleeding (not bone bleeding) occurs after drilling or tapping the first side, the VA may have been injured. The screw may still be placed but the contralateral hole and screw should not be placed. A post-op arteriogram is then performed to assess for propagating thrombus or dissection. Barring any contraindications, the procedure is repeated on the contralateral side. After screw placement, then posterior bone fusion (e.g. technique of Dickman and Sonntag, *see page 187*) is performed. External immobilization is usually not employed post-op (the screws are considered to supply adequate *internal* immobilization).

Results

A fusion rate of up to 99% with no complications has been reported[97]. Injury to the vertebral artery is the main potential complication.

C1-2 LATERAL MASS SCREWS

Placement of polyaxial mini screws in C1 lateral mass and C2 pedicle with rod fixation. Originated by Goel and Laheri[105] in 1994 and promulgated in 2001 by Harms and Melcher[106].

Advantages over C1-2 transarticular screws (*see above*):

1. the more superior and medial trajectory should reduce the risk of VA injury[106]
2. may be used in the presence of C1-2 subluxation
3. may be usable in certain cases of aberrant VA course
4. in selected cases, this can be used for temporary fixation without fusion (since joint spaces remain intact) and the hardware may be removed after an appropriate time to reclaim motion in the C1-2 articulation

Booking the case - C1-2 lateral mass fusion

Also see defaults & disclaimers (*page v*) and pre-op assessment (*see below*).

1. position: prone, pin headholder
2. anesthesia: awake fiberoptic or nasotracheal intubation
3. equipment: C-arm or O-arm image guidance
4. implants:
   A. mini-polyaxial screws (smooth shank screws needed for C1)
   B. cable required for interspinous graft (optional, but recommended)
5. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery to place screws & rods from the back of the neck to stabilize, and usually to fuse the top 2 bones of the neck
   B. alternatives: nonsurgical management in a collar, in some cases screws may be temporary and no fusion would be done
   C. complications: screw breakage/pullout, failure to fuse which might require addition surgery, loss of some neck bending motion is expected (≈ 20% is typical)

Surgical technique (excerpted highlights[106, 107])

NB: if fusion is to accompany screw placement (i.e. permanent screw placement), strong consideration should be given to supplemental interspinous

fusion (if not contraindicated) (*see page 187*) to prevent fatigue breakage of C1 screws.

Applied anatomy: there is no true neural foramen at C1-2, the C2 nerve root lies on the posterior surface of the capsule of the C1-2 articular joint.

Pre-op assessment: It is mandatory to know the position of the VA on both sides (and in particular, the location of both foramina transversarium of C1), and the following bony information (requires thin-cut CT scan):

1. cranio-caudal thickness (height) of the posterior arch of C1 (in case the arch needs to be drilled to facilitate screw placement)
2. to determine screw length: distance from the planned entry point (*see below*) to the planned exit target (midposition of the anterior part of the superior C1 VB)
3. to estimate medio-lateral angle for screws

Approach: Completely expose the C1–C2 complex. Dissect over the superior surface of the C2 pars interarticularis to expose the C1–C2 joint to accurately locate the entry point for the C1 lateral mass screws. Bleeding is controlled with bipolar cautery and/or Gelfoam soaked in thrombin. Complete exposure of the posterior face of the inferior C1 facet also disconnects the C2 root from the underlying attachments and facilitates it's inferior mobilization.

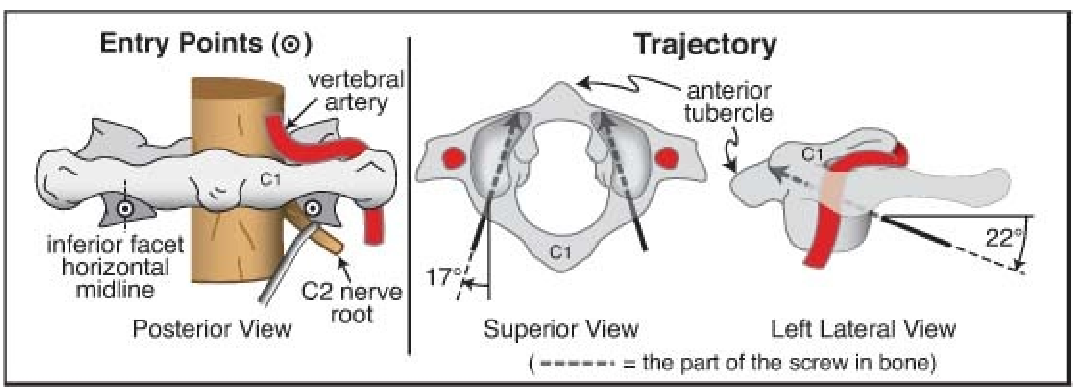

Figure 7-21 Screw entry point and trajectory for C1 lateral mass screws

1. **C1 lateral mass screws** ENTRY visualization commonly requires caudal retraction of the C2 dorsal root ganglion (occasionally this may not be feasible[107]; sacrificing the C2 root may be required but this can lead to post op pain and numbness[108]; technique is to divide the preganglionic nerve fibers and to close the dural defect[107]). The screw entry point is the midpoint of the inferior part of the C1 lateral mass (for both mediolateral

and cranio-caudal directions). An awl or a 1- to 2-mm high-speed drill is used to mark the position to prevent slippage while drilling the hole. Drilling a portion of the inferior arch of C1 is sometimes needed to allow screw placement (caution: the thickness of the arch in the cranio-caudal dimension varies widely, and the horizontal segment of the VA lies immediately above - use pre-op CT for planning)

2. **C1 screw** TRAJ averages ≈ 17° medially, ≈ 22° rostrally, TARGET the superior aspect of the anterior tubercle of C1 on lateral fluoro (*see Figure 7-21*)
3. **C1** SCREWS 3.5 or 4 mm diameter, length is determined from pre-op fine-cut CT to obtain bicortical purchase (✖ CAUTION: the ICA may be as close as 1 mm to the ideal exit site of the screw[109] ∴ some authors use only unicortical purchase). The screw needs to be proud to bring it up to the level of the C2 screw (it may actually be necessary to have the C1 screw protruding 1-2 mm more than the C2 screw in order to allow rod attachment[107]), and it should have an ≈ 8 mm un-threaded superficial portion to minimize irritation of the C2 nerve which could produce occipital neuralgia
4. C2 pedicle (pars) screws: placed as described on *page 187*
5. if a fusion is to be performed: the posterior arch of C1 and the C2 lamina are decorticated with a drill. Onlay fusion substrate is then placed, taking care not to compress the dura. Optional adjunct: intraarticular decortication and packing bone within the C1-2 joint

Post-op care

A cervical collar (soft or rigid, as preferred) for 4-6 weeks suffices.

INTERSPINOUS FUSION TECHNIQUE OF DICKMAN AND SONNTAG

A single bicortical graft is used, with multi-stranded cable passed sublaminar to C1 only. The bone graft is wedged between C1 and C2 (trapping it between loops of cable)[110, 111] (*see Figure 7-22*). Currently, this technique is infrequently used as the primary fixation for C1-2 fusion (unless technical difficulties prevent e.g. C1-2 lateral mass fusion). However, it may be most useful for limiting extension to offload C1 lateral mass screws to reduce the risk of screw breakage[112].

Cannot be used if the posterior ring of C1 or C2 is fractured.

Bone graft

Autologous bone is preferred. Bone is often taken from the posterior iliac crest (*see page 200*). A tricortical graft of ≈ 4 cm length and > 1 cm height is obtained. The top edged is removed to create a bicortical graft of ≈ 1 cm height.

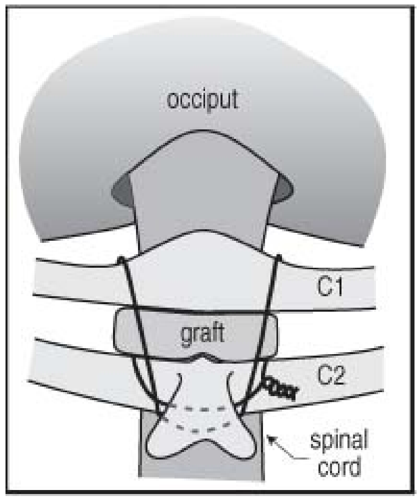

Figure 7-22 Dickman & Sonntag C1-2 interspinous fusion

7.8.4. C2 screws

Options:

1. pedicle screws (pars interarticularis screws): directed medially (*see below*)
2. lateral mass screws: directed laterally. Length is sized to fall short of foramen transversarium
3. C1-2 transarticular screws (*see page 184*): associated with more risk of VA injury
4. translaminar screws[113, 114]: 1 year stability appears to be less than C2 pedicle screws when used for subaxial fusions, but was ≈ as effective for axial fusions (C1-2 or C1-3)[115]. May be useful as a "bailout" for subaxial fusions when the C2 pars diameter is too small for pedicle screws[116]

C2 pedicle (pars) screws: Check CT scan or MRI to rule-out aberrant location of vertebral artery or unusual location of foramen transversarium before placing C2 pedicle screws. Some find image guided navigation systems to be helpful.

Technique:

1. ENTRY (*see Figure 7-23*) typically 3-4 mm above the inferior margin

of the C2 inferior facet, at the midpoint medio-laterally. Alternatively, use a location determined by palpating the pars with a Penfield 4, entering at the cranial and medial quadrant of the surface projection of the C2 pars[106]

2. TRAJ **20-30° medially** (through the central axis of the C2 pedicle)[117], **25° superiorly** (*see Figure 7-24*). To assist with trajectory, expose the proximal upper and medial border of the C2 pars interarticularis, and use a Penfield 4 to palpate during drilling (*see Figure 7-23*)
3. **procedure**: drill a shallow entry point, then drill with drill-stop set at 12 mm, monitoring progress at intervals under fluoro and palpating with probe, and if no breakout, then complete drilling by gradually increasing drilling depth by 2 mm increments until ≈ 30 mm depth is reached

- if withdrawal of the drill is followed by brisk bleeding, the screw should be inserted immediately to stop the bleeding. This bleeding may be from the vertebral artery; however, it is usually due to injury to the venous plexuses, and will not have any ill effects. In such cases it is best to not place the contralateral screw and to obtain an angiogram very soon postop

4. SCREWS **3.5 mm dia**. Screw length is not critical except when attempting to bridge a fracture gap (osteosynthesis) e.g. with a hangman's fracture in which case screws of 20-30 mm length are placed to avoid penetrating anterior C2 cortex (lag screws are used for this, or the proximal bone can be overdrilled); for most purposes screw lengths of 15-20 mm length are used

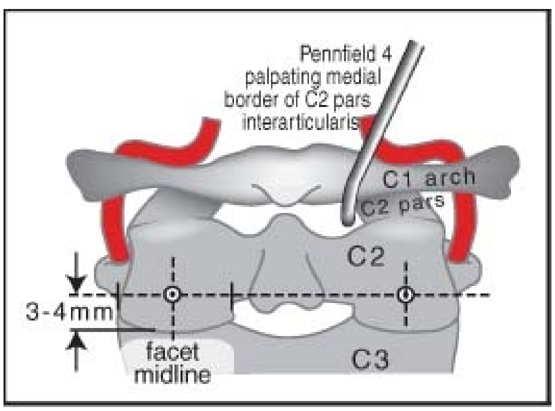

Figure 7-23 Entry point for C2 pedicle screw placement (posterior view)

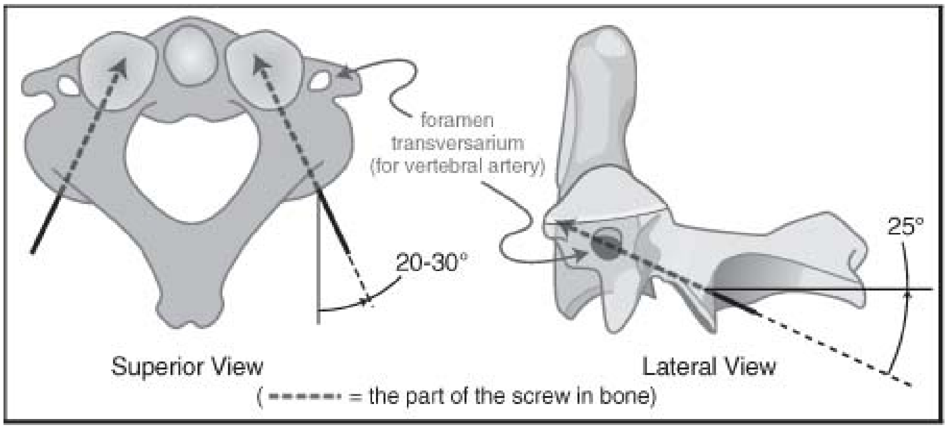

Figure 7-24 Screw trajectory for C2 pedicle screws

7.8.5. C3-6 fixation

LATERAL MASS SCREWS

May sometimes be used down to C7 (*see below*) or occasionally even T1 (*see below*).

Table 7-4 Comparison of methods for lateral mass screw placement for C3-6

Method	Entry point		Trajectory angle	
	Medio-lateral	Cranio-caudal	Medio-lateral	Cranio-caudal
An	1 mm medial to mid-point	midpoint	30° lateral	15° cephalad
Magerl	2 mm medial to midpoint	2 mm cranial to midpoint	20-25° lateral	parallel to facet joint*
Roy-Camille	midpoint	midpoint	0-10° lateral	0°

* angle can be determined by inserting probe into the joint

Technique:

A number of methods have been promulgated with various screw entry points and trajectories (some are shown in *Table 7-4*). Comparing 3 techniques[118] there was a lower risk of nerve injury with the following (method of An[119]):

1. ENTRY [119] **1 mm medial to the midpoint of the lateral mass** (*see Figure 7-25*). In the cranial-caudal direction, the midpoint is used. A Penfield 4 may be used to palpate the medial wall of the pars to help

determine entry point and trajectory

2. TRAJ **15° cephalad and 30° laterally** (*see Figure 7-25*)[119]. To get the lateral angulation, the holes are best drilled from the contralateral side of the patient, holding the drill shaft almost up against the spinous processes (if they are still present)

   A. SCREWS 3.5 mm diameter, 14-16 mm length (for C3-6)

   B. rod size: 3.5 mm diameter rods are usually used, and can be placed as far caudally as T3 as long as there is not gross instability (below T3, 5.5 mm diameter rods are used either via transitional rods or with rod connectors, e.g. "domino" connector)

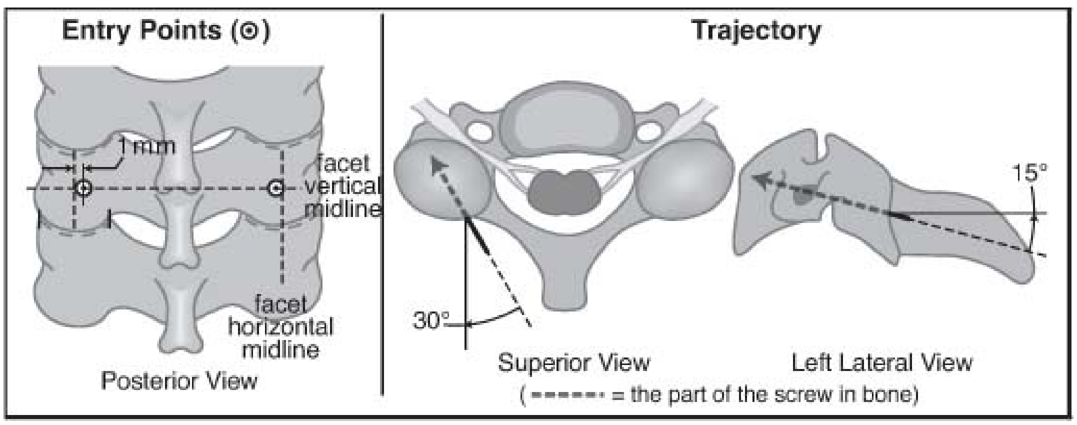

Figure 7-25 Screw entry point and trajectory for C3-6 lateral mass screws (method of An) 15°

Spinous process cables may optionally be used with intact spinous processes to help secure the bone graft[120].

TRANSARTICULAR SCREW FIXATION

An alternative to lateral mass fusion. First described in 1972 by Roy Camille. May be used alone or as an anchor point.

1. PROS:
   A. screws cross 4 cortical surfaces for better purchase
   B. compresses across the joint to promote fusion
   C. useful at cervico-thoracic junction where trajectory preserves facet capsule
   D. lower implant profile

2. CONS: cannot correct deformity
3. ENTRY midpoint of lateral mass
4. TRAJ perpendicular to joint, neutral to 5° lateral (to avoid VA and exiting root)
5. biomechanics: stability equivalent to lateral mass screws[121]
6. clinical: 25 patients (81 screws), 71 anchor, 10 fixation, 3.5 years F/U: solid fusion, no complications[122]

TRANSLAMINAR CERVICAL SCREW FIXATION

May be used in cervical or thoracic spine[123, 124].

1. indications: salvage technique when anatomy precludes pedicle screws
2. PROS:
   A. avoids complications related to pedicle screws
   B. no need for fluoroscopy (reduces radiation exposure)
3. CONS: requires intact posterior elements (cannot do with laminectomy)
4. ENTRY contralateral spinolaminar junction (at base of spinous process)
5. TARGET junction of the transverse process and the superior facet contralateral to the entry point
6. SCREWS 3.5-4.5 mm **x** 26 mm polyaxial screw
7. biomechanics: no data
8. clinical: 7 patients (C-T fixation), 14 months F/U, no hardware complications. Inconsequential ventral penetration in 5%[123]

7.8.6. C7 screws

C7 is a transitional level, and as a result either the lateral masses or the pedicles or both may be relatively small.

Screw fixation options:

1. **pedicle screws**: recommended especially when the C7 lateral mass is of inadequate size for lateral mass screws[119]. Placement with fluoroscopy may be difficult due to shoulder artifact on lateral fluoro, and direct visualization of the medial of the pedicle may be required as in the thoracic spine (*see page 190*)
2. **lateral mass screws** 117:

A. ENTRY as for C3-6 (*see above*)
B. TRAJ compared to C3-6 screws, slightly less lateral at ≈ 15° and a little less cephalad at ≈ 10°
C. SCREWS 3.5 mm diameter, 14 mm length

3. C7 transfacet screw[125]:
   A. PROS: reduced risk to spinal cord and nerve roots
   B. CONS: disrupts C7-T1 facet capsule, so T1 must be included in fusion. short screws result in low pullout strength ∴ may be best used as an intermediate anchor point and not an construct endpoint
   C. ENTRY 1-2 mm medial and superior to center of facet
   D. TRAJ 30° inferiorly and 20° laterally, TARGET goal is bicortical purchase
   E. SCREWS 3.5 mm diameter X 8-10 mm polyaxial screws
   F. biomechanics: equivalent to C7-T1 pedicle screws[126]
   G. clinical: 10 patients, long cervicalo-thoracic fixation, 6 months F/U, 3 patients with solid fusion

7.9. Surgical fusion of the thoracic spine

Pedicle screws

Preferable to lateral mass screws because the transverse processes (analogous to the lateral masses in the cervical spine) of most thoracic vertebrae are not as strong[120]. Thoracic pedicles are usually very narrow in the lateral dimension (the width is a little larger at the cranial end) and are very tall in cranio-rostral direction. Image guidance systems may also be helpful.

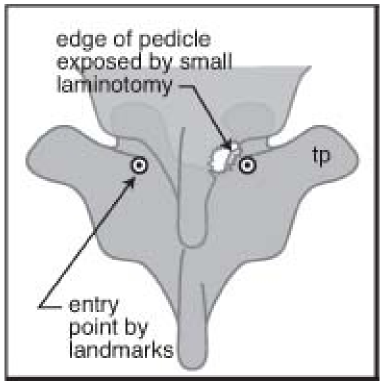

Figure 7-26 Entry point for thoracic pedicle screws (posterior view) tp = transverse process

Technique:

1. ENTRY medio-lateral: mid facet line. Craniocaudal: just where the superior facet joins the transverse process (*see Figure 7-26*). In the upper T-spine (above ≈ T5), because of the small pedicles and difficulty

visualizing the anatomy on fluoroscopy, the entry point and trajectory may be localized by palpating the medial and cephalad edges of the pedicle with a Penfield #4 dissector through a small laminotomy. If a single thickness rod or a transitional rod is being used, try to keep the entry points in line with cervical spine entry points. If a domino connector is being used to connect to a thicker rod, the entry point can be slightly lateral to those in the cervical spine.

2. TRAJ
   A. below T1: 5-10° medially and 10-20° caudad[120] (*see Figure 7-27*). A thoracic Lenke probe may be used as a pedicle finder.
   B. **T1**: if a lateral mass screw is placed at T1 (instead of a pedicle screw), aim almost straight down at the floor (with patient positioned horizontally, i.e. without Trendelenberg or reverse-Trendelenberg)
3. SCREWS smaller pedicles (usually T1-4, especially in females) usually require the smallest screw diameter (typically 4.5 mm). Others may accommodate 5.5 mm. Typical length: 20-25 mm

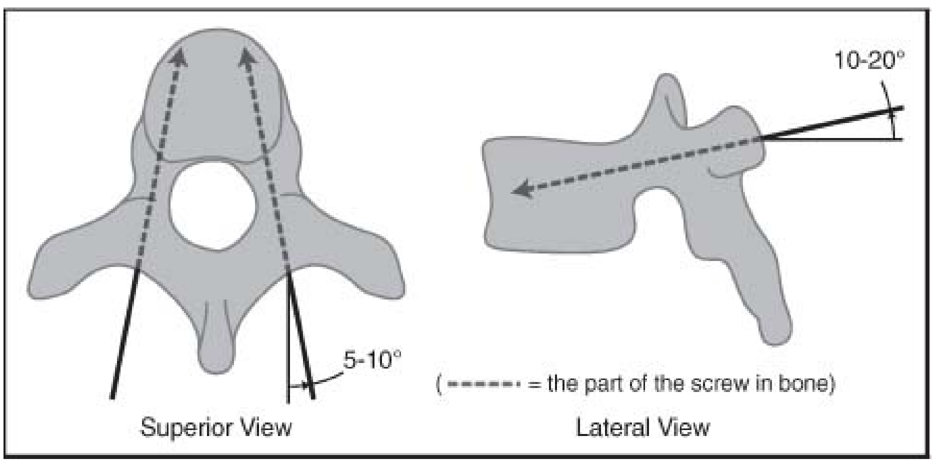

Figure 7-27 Screw trajectory for T1-T3 pedicle screws

4. **rod size**: when connecting to a cervical rod, down to ≈ T3 you can extend a 3.5 mm diameter cervical rod with some systems[A]. Below T3, ≈ 5.5 mm diameter rods (or 6.35 mm for scoliosis surgery) are usually used either via a transitional rod or using a domino connector to mate the two rods

A. e.g. Mountaineer by DePuy using a 4.35 diameter screw

7.10. Surgical fusion of the lumbar and lumbosacral spine

INSTRUMENTATION/FUSION PEARLS

1. a lumbar fusion that includes L1 should not be terminated at L1 or T12
2. the taller the disc space the less likely that posteriorly placed interbody grafts are well suited:
   A. the disc may not be significantly degenerated to require discectomy
   B. tall disc space means larger interbody implants which requires more retraction of nerve to insert (using a PLIF technique)
3. a long fusion should not be terminated at or near a vertebral level that is at the apex of scoliosis[127 (p 382)]
4. laminectomy without fusion should be avoided at the apex of scoliosis
5. posterior midline fusion: early experience with midline fusions resulted in lumbar spinal stenosis as a late complication. Therefore, current fusion techniques use postero-lateral fusion or interbody fusion (from anterior or posterior approach)

PEDICLE SCREWS

Pedicle screw pull out strength is determined in part by the major screw diameter which should be 70-80% of pedicle diameter (larger screws can break through the pedicle wall or can burst the pedicle). The minor diameter determines the strength of the screw and should be ≥ 5.5 mm in the adult lumbar spine. The length should allow penetration of 70-80% of the VB. Bicortical purchase or anterior VB penetration should be avoided to reduce the risk of injury to great vessels or abdominal viscera.

Open technique (*see below* for percutaneous placement):

1. ENTRY at the base of the transverse process, at the intersection of the center of the transverse process (in the rostral-caudal direction) and the sagittal plane through the lateral aspect of the superior facet. If a laminectomy has been performed at that level, the location of the pedicle is then verified by palpation using a probe within the spinal canal, otherwise fluoroscopy is used
2. TRAJ

A. the approximate mediolateral trajectory is shown in *Table 7-5*, and equals the lumbar vertebral number multiplied by 5° for each level from L1 to L5[128]. The angle of the screw in the rostral-caudal direction is determined by fluoroscopy, maintaining a course that is parallel to the vertebral end plate. A frameless stereotactic navigation system may help orient screw trajectory

B. **S2** screws are oriented laterally and superiorly and can be as long as 60 mm

3. SCREWS typical screw lengths vary from 40 to 55 mm (the goal is to cross ≈ 2/3 of the VB). S1 pedicle screws are usually only 35-40 mm long
4. rod diameter: typically 5-6.5 mm

X-ray verification once pedicle screws are placed: on AP view if the screw tip crosses the midline to the contralateral side, there is likely to be a breach of the medial pedicle (sensitivity 0.87, specificity 0.97, accuracy 0.98)[129], and if the screw does not pass medial to the medial pedicle wall there is likely to be lateral pedicle/VB violation (sensitivity 0.94, specificity 0.90, accuracy 0.96)[129]).

Table 7-5 Medial angles for lumbar pedicle screw

Level	Medial angle
L1	5° medially
L2	10° medially
L3	15° medially
L4	20° medially
L5 & S1*	25° medially
S2	40-45° laterally

* aim for sacral promontory

Percutaneous pedicle screws

The principles here are also employed in accessing the pedicles for e.g. vertebroplasty/kyphoplasty, percutaneous biopsy of pathology in the pedicle and/or vertebral body.

Basic principles:

1. requires AP and lateral fluoroscopy, or "O-arm" imaging (essentially an

image guided intraoperative CT scan). With fluoroscopy, biplane fluoro (1 C-arm dedicated for AP view, another for lateral) greatly expedites the procedure

2. this method can be employed essentially from T1 through S1 as long as adequate AP & lateral imaging of the involved level is possible. Using fluoro for upper thoracic placement (e.g. above ≈ T5) is challenging (small pedicles, and the shoulders interfere with x-ray)
3. the skin entry site is lateral to the lateral edge of the pedicle. This permits the needle to pass through the pedicle in a medial direction into the VB. The degree of angulation and therefore the distance off the midline for the entry site depends on the vertebral level being accessed (thoracic pedicles are oriented in a more AP direction, lumbar pedicles angulate medially inward) as well as the amount of overlying muscle/fat

Procedure

1. a needle, typically a Jamshidi needle, is place such that the tip is just short of entering the pedicle on the lateral fluoro (on left in *Figure 7-28*)
2. at this point, the needle tip should be at or just barely lateral to the lateral edge of the pedicle near the equator of the pedicle (on the right side, this would be at the "3:00" position, on the left side this would be at the "9:00" position)
3. the needle is advanced to just enter the pedicle on lateral fluoro, at this point it should be just within the pedicle margin at the 3:00 or 9:00 position (as shown on right in *Figure 7-28*)

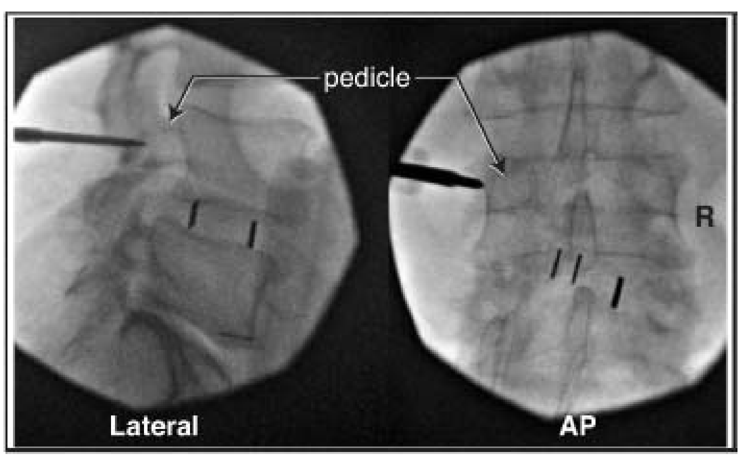

Figure 7-28 Pedicle cannulation - entering pedicle

4. continue advancing the needle into the pedicle. Intermediate fluoro images can be obtained (e.g. to monitor trajectory on the lateral fluoro), but the

next critical landmark is when the needle tip is just traversing the junction of the pedicle and the VB on the lateral fluoro (i.e. just entering the VB as shown on the left in *Figure 7-29*), it should be close to but never more medial than the medial border of the pedicleon the AP view (*see Figure 7-29*, right). If this criteria is maintained, the needle cannot breech the medial wall of the pedicle where it can threaten neural structures or compromise the purchase of the pedicle screw

5. subsequent steps differ for various procedures and manufacturers

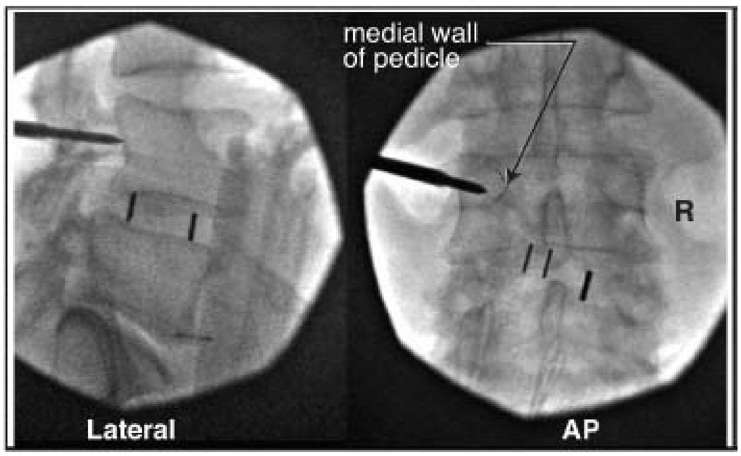

Figure 7-29 Pedicle cannulation - entering the vertebral body

Pedicle-screw rod diameters

Approximate weight guidelines for pedicle-screw rod diameters are shown in *Table 7-6*.

Table 7-6 Minimum recommended titanium rod diameter for lumbar pedicle-screw fixation

Patient weight		Rod diameter (mm)
(lbs)	(kg)	
30-90	12-40	4.5
90-225	40-100	5.5
> 225	> 100	6.35 (1/4 inch)

TRANSLAMINAR LUMBAR SCREW FIXATION

1. indications:
   A. short segment lumbar fusion

B. posterior component in a 360° fixation combined with interbody fusion

2. PROS:
   A. small incision, minimal soft tissue disruption
   B. decreased cost (fewer screws implanted)
   C. decreased blood loss
   D. adjacent facet joint spared
3. CONS:
   A. requires intact posterior elements (cannot use with laminectomy)
   B. cannot reduce
4. ENTRY skin incision 5-7 off midline, screw entry into bone in contralateral spinous process. Can be placed bilaterally
5. drill between the tables of the lamina across the center of the facet joint, terminating at the base of the transverse process
6. SCREWS 4.5 mm diameter fully threaded screws (no polyaxial head)
7. biomechanics: equivalent to bilateral pedicle screws[130]. Limited in extension[131]
8. clinical: 476 patients, 10 years mean F/U, 74% good outcomes[131]

POSTERIOR LUMBAR INTERBODY FUSION (PLIF & TLIF)

Bilateral laminectomy and aggressive discectomy followed by the placement of bone grafts into the decorticated disc space. It has been advocated to reduce the movement in an abnormal "motion segment" (defined as the area between two vertebra). Relatively contraindicated with well preserved disc-space height.

Many PLIFs when studied ≈ 1 year later show re-collapse of the disc space, which raises the question as to whether the PLIF has any benefit over simple discectomy.

Transforaminal lumbar interbody fusion **(TLIF)**: a variation on a PLIF where the graft is placed from one side (via the "neural foramen) after complete removal of the facet joint on that side. Requires much less nerve root retraction than PLIF, and is often advantageous for re-operations where going through the foramen avoids the scar tissue.

Stand-alone PLIFs or TLIFs may be associated with progressive spondylolisthesis at that level and are usually supplemented with pedicle screws/rods.

LATERAL LUMBAR INTERBODY FUSION (LLIF)[132]

Trademarked names include "extreme-lateral" **(XLIF™)** or "direct-lateral" lumbar interbody fusion **(DLIF™)**. A retroperitoneal approach. Indirectly decompresses nerves by distracting the disc space. Indicated for some cases of spinal stenosis (in patients who have had previous posterior spine surgery in the same area, the LLIF avoids the difficulty of dealing with scar tissue and the inherent increased risk of CSF leak from dural tear), can also correct some scoliosis and can be used to remove damaged or malpositioned lumbar disc replacement devices[133]. The need for additional stabilization (e.g. with a lateral plate, or facet screws, or pedicle screws (unilateral or bilateral) is not yet resolved, and may not be needed in all cases. For cases without instability, a lateral plate applied through the same exposure when it can be done should suffice. If there is instability, posterior stabilization with facet screws or pedicle screws are recommended. Access is best from L1-5. For L1-2, one can retract the 12th rib, or go between 11th & 12th rib, or excise the 12th rib. Iliac crest prevents access to L5-S1 (axial-LIF may be used here) and occasionally to L4-5 (*see below*). Above T11, enter on right (check pre-op MRI for anomalous position of aorta). ✖ With <u>thoracic</u> lateral interbody fusions, DO NOT penetrate the contralateral anulus. Difficult in grade II or higher spondylolisthesis. Intraoperative EMG monitoring is critical, so anesthesiologist needs to use only <u>short-acting</u> neuromuscular blockage at beginning of case. In males, implants are typically 55 mm in length (oriented along patient's lateral axis) if placed in the midposition of the VB, or 45 mm in the anterior portion (lengths are 10% shorter in females)[134].

Contraindications:

1. cases requiring direct decompression
2. prior retroperitoneal surgery on the planned side of LLIF (can still be done on contralateral side, sometimes may still be feasible on ipsilateral side)
3. cannot access L5-S1 (NB: a sacralized L5 may cause the L5-S1 disc space to look like L4-5 and may not be accessible)
4. may not be able to access L4-5 if the iliac crest extends more than ≈ halfway up the L4 VB. Sometimes it is necessary to position the patient on the O.R. table with the table flexed and a bump under the hip to see if the space will "open up" and permit access
5. anomalous vascular anatomy interfering with approach: check position of great vessels on pre-op MRI

Relative contraindications:

1. osteoporosis: may also be contraindication to lateral plates
2. active infection
3. “pinpoint” central canal stenosis (some of these cases can still respond)

Complications:

1. thigh numbness: due to genitofemoral nerve trauma: cannot be monitored with EMG. Usually transient, resolves in ≈ 2 weeks
2. thigh flexion weakness: due to psoas injury. Risk increases if > 2 levels are done. Usually transient, resolves in 1-8 weeks
3. quadriceps weakness: due to nerve root/plexus injury (probably from psoas retraction - shorter operations may have lower risk) or psoas hematoma. Onset may be delayed 1-2 d post op. Incidence < 1%. May improve slowly over a long time (> 9 months)
4. vascular injuries

Booking the case - lateral interbody fusion

Also see defaults & disclaimers (*page v*) and pre-op orders (*see below*).

BOOKING

1. position: lateral decubitus, typically left-side up unless specified otherwise
2. equipment: C-arm
3. implants: interbody graft. For spondylolisthesis: pedicle screws may be needed, alternatively, interspinous clamps may be used
4. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the side to place a spacer between two of the vertebrae (backbones) to make more space for the nerves and to stop painful movement, screws/plates etc. will then need to be placed either from the side through the same opening or sometimes from the back
   B. alternatives: nonsurgical management, open surgery through the back
   C. complications: thigh weakness (usually temporary), knee weakness (uncommon), thigh numbness, graft subsidence/migration, failure to achieve desired relief

ANTERIOR LUMBAR INTERBODY FUSION (ALIF)

Relatively contraindicated in males because of risk of retrograde ejaculation in 1-2% (as high as 45% in some reviews). Other risks: injury to great vessels,

especially with calcified arteries, especially at L4-5.

AXIAL LUMBAR INTERBODY FUSION (AX-LIF)

Axial lumbar interbody fusion (Ax-LIF) AKA AxiaLIF™ (by TranS1). Initially developed for indirect decompression at L5-S1, can be extended to include L4-5 with L5-S1 in patients with favorable anatomy (permitting a straight trajectory from tip of coccyx through L5-S1 and L4-5). Minimally invasive through incision in gluteus, threaded spacer is inserted through the S1 vertebral body across the disc space. Differential thread pitches produce disc-space distraction. Not intended as a standalone, supplemental fixation (*see below*) provides the required rotational stability:

1. if facets and pars are intact: can use percutaneous facet-pedicle screws (*see below*) for a single level (L5-S1)
2. if bilateral pars defects, or for a 2-level Ax-LIF, pedicle screws/rods (placed open or percutaneously) are recommended (especially in heavier patients)
3. spinous process clamp(s)

Booking the case - axial lumbar interbody fusion

Also see defaults & disclaimers (*page v*) and pre-op orders (*see below*).

1. position: prone, with the knees dropped <u>below</u> the level of the hips (e.g. either a Jackson or Andrews table, or OSI table with a sling to permit the knees to drop)
2. equipment: 2 C-arms for biplane fluoro (required)
3. implants:
   A. TranS1 AxiaLIF™ and facet screws (i.e. trans-facet pedicle screws)
   B. for 2-level Ax-LIF or if pars defect: also schedule a separate vendor for per-cutaneous pedicle screws/rod
4. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: minimally invasive surgery to place a screw to increase the space around the nerves and to stabilize the spine using an incision near the tail-bone, combined with surgery through the back to place screws and possibly short rods
   B. alternatives: nonsurgical management, open surgery on the back
   C. complications: (usual spine surgery complications - *see page v*), bowel

injury (0.6% risk) which could necessitate a (temporary) colostomy

Pre-op:

1. MRI of the lumbar spine without contrast (or CT if MRI contraindicated) that goes all the way down through the tip of the coccyx with axial, sagittal and coronal views. Assesses whether a workable trajectory can be achieved (*see below*), also rule's out Tarlov's cyst, low aortic bifurcation, large midline vessels at S1-2 or other vascular anomalies
2. bowel prep the day before surgery: (reduces bacterial count and decompresses the rectum) e.g. GoLytely 4 L po (drink 8 oz every 15 minutes), or MagCitrate for patients with chronic constipation. ✖ Do not use Fleets Phospo-Soda if renal insufficiency (risk of acute phosphate nephropathy) or if CHF
3. pre-op antibiotics prior to skin incision. One of the following regimens:
   A. ertapenem (Invanz®) 1 gm IV
   B. cefazolin (Kefzol®, Ancef®) + metronidazole (Flagyl®)[135], or, if ß-lactam allergic, then metronidazole + (ciprofloxacin 500 mg IV or levofloxacin 750 mg IV)[135]
   C. cefoxitin (Mefoxin®) 2 gm IV 30-60 minutes pre-op, repeat q 6 hours **x** 24 hours post-op

✖ Contraindications:

1. vascular: aortic bifurcation below L5-S1 disc space or large midline vessels at S1
2. prior retroperitoneal surgery (renal surgery, proctectomy,) AP resection, low anterior resection, history of pelvic XRT e.g. for cancer of rectum, anus or prostate)
3. severe sacral lordosis/hook-like coccyx may prevent this approach (assess trajectory on pre-op planning to determine if patient is a candidate for this)
4. relative contraindications: Crohn's proctitis, ulcerative colitis, diverticulitis, full-thickness rectal prolapse
5. use in osteoporotic patients has not been evaluated

Technique

Details will not be covered here. Some points of importance:

1. setup: biplane fluoro is required
2. patient position: prone, with the knees dropped below the level of the hips

3. skin ENTRY point: 1 cm lateral to the tip of the coccyx, 1-2 cm caudal to the paracoccygeal notch
4. bone entry point: at the S1-S2 interspace in the midline
5. TRAJ (the manufacturer's template may help):
   A. for a single level (L5-S1) Ax-LIF: the trajectory should pass through the L5-S1 disc at about the midpoint of the AP diameter of the disc
   B. for a 2-level Ax-LIF: the trajectory usually passes through the anterior third of the L4-5 disc (*see Figure 7-30*)
6. grafting usually employs a mixture of (optional) rhBMP together with granules of tricalcium phosphate and hydroxyapatite

Complications

Bowel perforation: This complication, while not unique to this procedure, is most often considered in the context of this operation. Incidence is 31/5290 procedures (0.6%) according to TranS1 company literature. A high (intraabdominal or intraperitoneal) rectal perforation will present with findings of an acute surgical abdomen (abdominal pain, fever, tachycardia, hypotension, signs of peritonitis = rigidity/guarding, elevated WBC, free air on abdominal x-ray). Patients with a low (extraperitoneal/retroperito-neal) injury are not as ill on presentation and may have malaise, low-grade fever, and possibly bloody or purulent anal discharge.

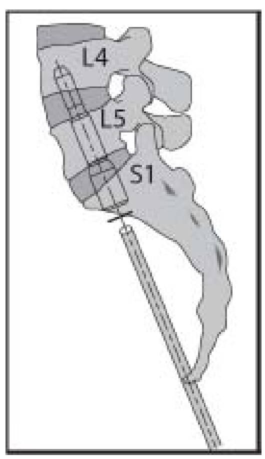

Figure 7-30 Schematic showing a favorable trajectory for a 2-level

Management of rectal perforation:
1. if suspected at the time of surgery:
   A. with the patient still in the jack-knife position a flexible or rigid

sigmoidoscopy can identify most injuries

B. alternatively, 100-200 cc of Gastrografin® can be instilled into the rectum via a Foley catheter, and fluoroscopy is used to visualize 360° of the rectum (using AP and lateral views). The patient may need to be placed in Trendelenburg to get the contrast to contact the dorsal rectum

C. abdominal CT scan (the most sensitive test for free air) or CXR: free air under the diaphragm indicates peritoneal compromise, but with AxiaLIF does not necessarily mean bowel perforation

2. if bowel injury is suspected hours to days post-op, order either:
   A. abdominal and pelvic CT using rectal Hypaque®/Gastrografin®[136]
   B. alternatively, a Hypaque/Gastrografin enema with x-ray or fluoro imaging

If rectal perforation is demonstrated:

1. make patient NPO and start IV fluids
2. broad spectrum IV antibiotics are started immediately
3. STAT general surgery consultation: make sure the surgeon understands the procedure so he will know where to look for the injury. A diverting colostomy (often temporary) may be required. A handful of patients with no systemic or peritoneal signs of infection have been managed with antibiotics, bowel rest and close observation

TRANSFACET PEDICLE SCREWS

Screws place directly across the lumbar facet joint into the pedicle of the level below. No rod is needed. Immobilizes only, does not provide any decompression, distraction or fusion. Therefore not intended for use as a standalone. Can be placed percutaneously.

Indications

Placement is optimal for L3-4, L4-5 or L5-S1. Difficulty increases in upper lumbar levels.

May be used as adjunct to:

1. ALIF
2. LLIF (when lateral plate not used)
3. contralateral to TLIF (pedicle screws could be used on the side of the TLIF, or a spinous process clamp could be used)
4. axial-LIF (Ax-LIF)

Contraindications

A transfacet pedicle screw cannot be used where the facet has been removed (e.g. for a TLIF) or with a pars defect in the upper of the two levels to be fused.

Technique

1. placed percutaneously or via an open procedure usually in the prone position
2. approximate skin incision site: a single midline ≈ 1.5 cm vertical incision is used
   A. for L5-S1 or L4-5: incision at L3 spinous process
   B. for L3-4: incision at L2 spinous process
3. use AP & lateral fluoro to guide trajectory
   A. AP fluoro: lay a guidewire on the patient's back and orient it to pass through the desired pedicle. Use a skin marker on the patient's back to mark the guidewire's trajectory
   B. lateral fluoro: initial bony target is the midpoint of the inferior facet of the upper level. The tip of the guidewire should contact the bone directly posterior to the inferior endplate of the upper level

FACET FUSION

A bone dowel (e.g. TruFUSE® by MinSURG) is placed into a predrilled opening in the facet joint to promote fusion across the joint. Marketed as a possible standalone.

S2 SCREWS

May be directed medially (analogous to pedicle screws), or more commonly, directed laterally and superiorly into the ala. In either case, bicortical purchase is necessary.

The main structure to avoid is penetrating the sacroiliac **(SI)** joint with the screw.

ILIAC SCREWS

Wide exposure is needed. On the initial few cases, the surgeon may be better served by exposing all the way to the posterosuperior aspect of the sciatic notch so that the screw trajectory can be aimed using a palpating finger.

A small amount of bone is removed just below and medial to the posterior

superior iliac spine. This prevents the head of the screw from being too superficial which may cause discomfort or skin breakdown. An offset adapter is usually required to connect to rods passing through pedicle screws in the levels above.

TARGET Aim towards the acetabulum to pass approximately 1 cm superior to the sciatic notch on AP fluoro. Avoid penetrating the cortex, especially in the sciatic notch.

SCREWS Length 50-70 mm (the screw should end just above midpoint of the the sciatic notch, or a little medial to that). Diameter: 6-8 mm.

7.11. Bone graft

7.11.1. Use of bone graft extenders/substitutes as an adjunct to fusion

PRACTICE GUIDELINE 7-1 BONE GRAFT EXTENDERS & SUBSTITUTES

Level I[137]: autologous bone or recombinant human bone morphogenic protein (rhBMP-2) bone graft substitute is recommended in the setting of an ALIF in conjunction with a threaded titanium cage

Level III[137]:

- rhBMP-2 in conjunction with hydroxyapatite and tricalcium phosphate may be substituted for autograft in some cases of posterolateral fusion
- calcium phosphate is recommended as a bone graft extender, especially when combined with autologous bone

Assessing surgical lumbar fusion: See *PRACTICE GUIDELINE 7-2*.

PRACTICE GUIDELINE 7-2 RADIOGRAPHIC ASSESSMENT OF FUSION

Level I[138]: static x-rays alone are not recommended

Level II[138]:

- in the absence of rigid instrumentation, lack of motion between vertebrae on lateral flexion/extension x-rays is highly suggestive of successful fusion

✖ technetium-99 bone scanning is not recommended

Level III[138]: radiographic techniques, often in combination, may be used when failed lumbar fusion is suspected, including: static and flexion/extension x-rays, CT scan

PRACTICE GUIDELINE 7-3 CORRELATION BETWEEN FUSION & OUTCOME

Level III[139]: the correlation between fusion and clinical outcome is not strong, and in any given situation fusion status may be *unrelated* to outcome

7.11.2. Bone graft properties

Used mostly for spine fusions. Components of bone graft that are important for fusion:

1. **osteoinduction**: recruitment of mesenchymal cells and the stimulation of these cells to develop into osteoblasts and osteoclasts
2. **osteogenesis**: formation of new bone by host or graft mesenchymal stem cells transformed into osteoblasts
3. **osteoconduction**: the structure of the graft that acts as a scaffold upon which new bone and blood vessels form
4. mechanical stability: the structural anatomical biomechanical support provided, e.g. following discectomy, corpectomy or resection of vertebral tumor

Table 7-7 summarizes the properties of various bone graft materials (adapted[196-198]). See the sections that follow for more details.

Table 7-7 Characteristics of bone graft materials (see text for details)

Material	Mechanical stability	Osteogenic	Osteo-inductive	Osteo-conductive
Cancellous autograft	±	++++	++	++++
Cortical autograft	+++	+	+	+
Vascularized autograft	+++	+++	++	+++
Allograft	+	–	±	+
Bone marrow aspirate	–	+	±	+
Demineralized bone matrix (DBM)	–	–	+	+
Bone morphogenic protein (BMP)	–	–	++++	–
Collagen	–	–	–	–
Ceramics	+	–	–	+++

Key: – no effect, ± minimal or no effect, + mild, ++ moderate, +++ strong, ++++ very strong effect

Autograft: Common donor sites: iliac crest, rib[199], fibula, bone removed during decompression. Characteristics:

1. PROS: no histocompatibility or disease transmission issues
2. CONS:
   A. persistent post-op donor site pain: occurs in as many as 34% of patients (the severity of which was graded as “unacceptable” in 3%)[200]
   B. increased surgical risks of:
      1. blood loss
      2. wound infection
      3. fracture
      4. cosmetic deformity
      5. increased operative time to procure
      6. numbness from nerve injury (e.g. cluneal nerves *see below*)
      7. hematoma
3. subtypes
   A. cancellous bone: provides all graft components except mechanical stability
   B. cortical bone:
      1. provides superior and immediate mechanical strength
      2. has diminished osteoinduction and osteoconduction capacity
   C. corticocancellous bone: e.g. tricortical iliac crest wedge. Contains all bone graft components
   D. vascularized autograft:
      1. technically challenging
      2. best suited for areas that are scarred, irradiated, or that span long segments
   E. autologous bone marrow:
      1. source of osteoprogenitor cells and osteoinductive substrates
      2. diminished donor site risks
      3. no osteoconductive nor structural properties

Allograft: Acquired through organ procurement agencies. Primarily frozen or freeze dried. Donor sites include: ilium, tibia, fibula, femur, rib.

1. PROS: eliminates risks associated with harvesting autograft
2. CONS:
   A. small but real risk of disease transmission
   B. provide only osteoconduction (lacks osteoinduction and osteogenesis)
   C. availability may vary from time-to-time

3. subtypes
   A. tricortical block, bicortical plug, or unicortical dowel
   B. corticocancellous: matchsticks, crushed
   C. cancellous: cubes, block, crushed, bone powder
4. uses: allografts are acceptable for structural grafts such as in anterior spinal interbody fusion, where compressive forces are applied to the graft. However, for onlay grafts such as for posterior cervical fusion, the lack of osteoinductive and osteogenetic properties is a critical shortcoming

Demineralized bone matrix (DBM): Prepared by acid extraction, reducing antigenicity, but preserving some osteoconductive and variable osteoinductive properties.

1. available as putty, gel, chips, granules or powder
2. primarily used as an adjunct to other grafting materials
3. CONS:
   A. increased cost
   B. variable efficacy between preparations and batches of the same preparation
   C. no mechanical or structural properties

Bone morphogenic proteins (BMP): (AKA bone morpho *genetic* proteins). Biological compounds that induce the transformation of mesenchymal stem cells into osteoblasts (osteoinduction) with the potential to induce ectopic bone formation. There are ≈ 20 different proteins from the transforming growth factor-ß family. Produced using recombinant DNA technology.

1. a carrier matrix is required to retain the soluble factor at the graft site (i.e. to prevent the BMP from diffusing into adjacent tissues, thereby reducing the desired effect and possibly inducing bone growth at undesired foci)
2. FDA approved in U.S. only for ALIF. Other uses are "off label"
3. available preparations: rhBMP-2 (Infuse® by Medtronic)
4. PROS: increases fusion rates
5. CONS:
   A. expensive
   B. ectopic bone formation, bone resorption (so-called osteolysis) or remodelling at the graft site[201]
   C. in anterior cervical spine surgery: neck swelling with airway compromise, hematoma, painful seroma[201]

Collagen: Used primarily as a carrier for other osteoinductive, osteoconductive, or osteogenetic materials and as a composite with other graft extenders

1. PROS: contributes to vascular ingrowth, mineral deposition, and growth factor binding
2. CONS:
   A. minimal structural support
   B. potential immunogenicity

Ceramics: Includes tricalcium phosphate, calcium carbonate & hydroxyapatite.

1. PROS: no risk of disease transmission
2. CONS: only recommended for use as bone graft extenders (i.e. must be combined with autograft, bone marrow aspirate, BMP…)

7.11.3. Bone graft procurement

ILIAC CREST

ANTERIOR ILIAC BONE GRAFT

Should be obtained at least ≈ 3-4 cm lateral to the anterior superior iliac spine **(ASIS)** to avoid the lateral femoral cutaneous nerve and to reduce the risk of avulsion fractures of the remaining ilium. When a tricortical graft is taken, keep the dissection in the subperiosteal plane and avoid electrocautery on the medial (inner) surface when detaching the iliacus muscle to avoid injury to the ilioinguinal, iliohypogastric and lateral femoral cutaneous nerves.

POSTERIOR ILIAC CREST BONE GRAFT

May be used to obtain corticocancellous strips or plates for onlay bone grafts, or tricortical grafts which may be used as strut grafts or for C1-2 arthrodesis.

Posterior bone grafts are taken from the medial 6-8 cm of the iliac crest to avoid the superior cluneal nerves (which cross the posterior iliac crest ≈ 8 cm lateral to the posterior superior iliac spine) with resultant buttock numbness or the development of painful neuromas. A vertical incision just medial to the posterior superior iliac spine usually works well.

The spine may sometimes be found on corpulent patients by locating the "dimple of Venus" (fossae lumbales laterales - indentation sometimes visible superior to the gluteal cleft, directly superficial to the sacroiliac joint) and

incising slightly lateral to it. Avoid mistaking the sacrum for the iliac spine.

The gluteus maximus is dissected off the lateral surface subperiosteally. To avoid fractures extending into the iliac crest, a wide osteotome should be used to create a “stop cut”; alternatively, a sagittal saw may be used. Avoid penetration through the inner cortical surface of the crest so as not to enter the pelvis and possibly cause an intraabdominal hematoma. Another potential complication is fracture extension into the greater sciatic notch with possible injury to the gluteal arteries and sciatic nerve among others. Once the graft is removed and cancellous bone is gouged out, the exposed bone surfaces should be waxed and closed system drainage should be used to reduce the risk of local hematoma formation.

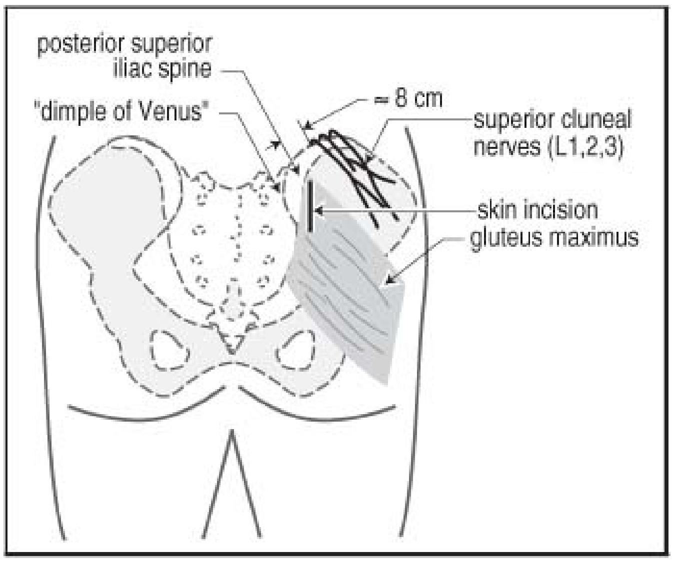

Figure 7-31 Posterior iliac crest bone donor site

FIBULA

Autogenous fibular graft provides a high arthrodesis rate[202], but may be associated with significant morbidity, and so may be best reserved for salvage procedures[203]. Preserve the proximal fibular head to avoid injury to the peroneal nerve. At least 7 cm of distal fibular should be maintained to preserve ankle stability[199].

7.12. Percutaneous access to the CSF

7.12.1. Percutaneous ventricular puncture

Indications

In pediatrics, may be used to remove hemorrhagic ventricular fluid following intraventricular hemorrhage, or to obtain CSF specimen in cases of suspected ventriculitis. May be used emergently in pediatrics or adult as a temporizing measure in patient herniating from obstructive hydrocephalus.

Peds

Shave hair. 5 minute Betadine® prep.

The right side is preferred. Enter through coronal suture just lateral to anterior fontanelle **(AF)** using a 20-22 Ga. spinal needle. If a CT scan has been done, it may be used to help judge angulation (usually varies between contra- and ipsilateral medial canthus and intersection with EAM).

Adult[140]

Only used emergently. Takes advantage of thin orbital roof in adult.

Prep conjunctiva and skin with antiseptic (e.g. ophthalmic betadine). Elevate the eyelid and depress the globe. Using a 16-18 Ga. spinal needle, penetrate the anterior third of orbital roof (1-2 cm behind orbital rim) with firm pressure (may need gentle tapping). Aim at coronal suture in the midline. The frontal horn should be about 3-4 cm deep.

7.12.2. Subdural tap

Indications

Utilized in pediatrics. Used to be done for diagnostic purposes, but this has been supplanted by CT, MRI & ultrasound. Currently, this procedure may be used emergently for decompression, to drain subdural collections and to obtain fluid for diagnostic tests, such as culture (repeat taps may be used, but surgery should be considered after ≈ 5-6).

Technique

Shave hair. Prep 5 minutes with povidone iodine (Betadine®). Using a short 20-21 Ga. spinal needle (spinal needle is recommended because the stylet may

reduce the risk of implanting epidermal cells into the CNS), penetrate the lateral margin of the anterior fontanelle **(AF)** or coronal suture at least 2 cm off midline. Remove the stylet and aspirate. With bilateral fluid collections, bilateral taps should be done.

7.12.3. Lumbar puncture

Contraindications

1. known or suspected intracranial mass } risk of tonsillar herniation (*see below*)
2. non-communicating hydrocephalus } risk of tonsillar herniation (*see below*)
3. infection in region desired for puncture: choose another site if possible
4. coagulopathy
   A. platelet count should be > 50,000/mm^3 (*see page 34*)
   B. patient should not be on anticoagulants because of risk of epidural hematoma (*see page 515*) or subarachnoid hemorrhage[141] with secondary cord compression
5. use caution in suspected aneurysmal SAH: excessive lowering of the CSF pressure increases the transmural pressure (pressure across the aneurysm wall) and may precipitate rerupture
6. caution in patients with complete spinal block: 14% will deteriorate after LP[142]

- elevated ICP and/or papilledema by themselves are NOT contraindications (e.g. LP is actually used diagnostically and as a treatment in idiopathic intracranial hypertension, *see below*)

Technique

Background and anatomy

The spinal cord and column are the same length in a 3-month fetus. After that, the spinal column grows faster than the cord. As a result, the conus medullaris is located rostral to the termination of the thecal sac in the adult, situated between the middle thirds of the vertebral bodies of L1 and L2 in 51-68% of adults (the most common location), T12-L1 in ≈ 30%, and L2-3 in ≈

10% (with 94% of cords terminating within the territory of L1 and L2 vertebral bodies)[143]. The thecal sac ends ≈ S2. The **intercristal line** (connecting the superior border of the iliac crests) crosses the spine at the L4 spinous process or between the L4 and L5 spinous processes in most adults.

Procedure

Position: the procedure is usually performed in the lateral decubitus position. As the needle is advanced, it is helpful to have the patient bring the knees up and to flex the neck in order to open up the spaces between the posterior elements of the spine.

For diagnostic LP, a 20 Ga spinal needle is often selected. Larger needles (e.g. 18 Ga) may be used e.g. with pseudotumor cerebri to encourage post-procedure drainage of CSF into the soft tissues of the back.

The back is prepped and draped to create a sterile working area.

Entry point: in an adult, use the L4-5 interspace in most cases (located at or just below the intercristal line) or 1 level higher (L3-4). Peds: L4-5 is preferred over L3-4.

The needle is always advanced with the <u>stylet in place</u> at least through the skin and some subcutaneous tissue to avoid introducing epidermal cells which may cause iatrogenic <u>epidermoid tumors</u> (see *Complications following LP* below). The needle is aimed slightly cranially (to parallel the spinous processes) and usually a little down towards the bed (aiming towards the umbilicus). If a Quincke LP (standard) needle is used, the bevel is turned parallel to the length of the spinal column to reduce the risk of post-LP H/A (see *needle type*, page 204). In general, if bone is encountered it is more often due to deviation from a true midline trajectory rather than a failure to aim correctly in the rostral-caudal direction. The needle should be withdrawn to just below the skin surface before attempting a new trajectory.

If during insertion of the needle the patient experiences pain radiating down one LE, this usually indicates that a nerve root has been encountered. The needle should be withdrawn immediately and reinserted aiming more towards the side <u>contralateral</u> to the extremity that experienced the pain. The stylet is removed at intervals during the insertion to look for CSF (a distinct pop is sometimes felt as the needle penetrates the dura).

Once CSF flows, the needle is connected to a manometer through a 3-way stopcock, the pressure is measured and recorded (*see below*), and CSF is drained into sterile tubes (1-2 ml for each tube) for laboratory analysis (*see below*). The practitioner should also note the color of the fluid (clear, blood tinged,

xanthochromic…) and the clarity (clear, cloudy, purulent…).

At the end of the procedure, the stylet should be replaced before the needle is withdrawn (to reduce post-LP H/A, *see below*).

Opening pressure

The opening pressure **(OP)** should be measured and recorded for every LP. To be meaningful, the patient should be lying down and as relaxed as possible (should not be in forced fetal position), with the bed flat. The variation of pressure with respirations is usually a good indication of a communicating fluid column (the fluctuation is inphase with the respiratory pressures in the inferior vena cava, rising with inspiration and falling with expiration[144]). **Normal values**: in the left lateral decubitus position, average OP = 12.2 ± 3.4 cm H_2O (8.8 ± 0.9 mm Hg)[145]. Also, see *Table 14-1*, page 297 for peds.

Queckenstedt's test: if a subarachnoid block is suspected (e.g. from spinal tumor), compress the jugular vein **(JV)** first on one side then on both (do not compress carotid arteries). If there is no block, the pressure will rise to 10-20 cm of fluid, and will drop to the original level within 10 seconds of release of the JV[146 (p 11)]. Do not do JV compression if intracranial disease is suspected.

Laboratory analysis

Routinely, three tubes are sent for analysis as shown in *Table 7-8*. See *Table 14-5*, page 299 for interpreting the results of the laboratory analysis.

If the tap is possibly *traumatic* (i.e. bloody), or if having an accurate cell count is essential (e.g. to R/O SAH) then 4 tubes are collected, and the first and last are sent for cell counts and are compared (see *Traumatic tap*, page 298).

If special cultures are required (e.g. acid fast, fungal, viral) they are also specified on the tube for culture & sensitivity (C & S).

If CSF for *cytology* is desired (e.g. to R/O carcinomatous meningitis or CNS lymphoma), then at least 10 ml of CSF must be sent in one tube to pathology.

Table 7-8 Routine tests for CSF

Test	If there is no concern about possible traumatic tap	If there is concern about traumatic tap
cell count		Tube 1
gram stain + C & S	Tube 1	Tube 2
protein and glucose	Tube 2	Tube 3
cell count	Tube 3	Tube 4

COMPLICATIONS FOLLOWING LP

The overall risk of disabling or persistent symptoms (defined as severe H/A lasting > 7 days, cranial nerve palsies, major exacerbation of pre-existing neurological disease, prolonged back pain, aseptic meningitis, and nerve root or peripheral nerve injuries) has been estimated at 0.1-0.5%[147]. Severe side effects, which include brainstem herniation, infection, subdural hematoma or effusion, and SAH, are rare[148 (p 171-2)].

Possible complications include:

1. tonsillar herniation
   A. acute herniation in the presence of mass lesion (*see below*)
   B. chronic tonsillar herniation (acquired Chiari 1 malformation): reported after multiple traumatic LPs with presumed post-LP CSF leak[149]
2. infection (spinal meningitis)
3. "spinal headache": usually positional (diminishes with recumbency) (*see below*)
4. spinal epidural hematoma: usually seen only with coagulopathy (*see page 515*)
5. spinal epidural CSF collection: may be fairly common in patients with post-LP H/A. Usually resolves spontaneously
6. epidermoid tumor: risk may be increased by advancing LP needle without stylet (transplanting a core of epidermal tissue)[150-152]
7. impinging nerve root with needle: usually causes transient radicular pain, may cause permanent radiculopathy in some
8. <u>intracranial</u> subdural hygroma or hematoma[153, 154] (rare)
9. vestibulocochlear dysfunction[155]:
   A. subclinical (demonstrated on audiogram) or moderate reduction in hearing may occur, and seems to correlate with post-procedure CSF leakage
   B. sudden hearing loss may occur. Perform audiogram to quantify loss. Treat with bedrest for several days, prednisone 60 mg/d tapered over 2-3 weeks
   C. pathogenesis: reduced CSF pressure may reduce perilymph pressure through the cochlear aqueduct[156], producing endolymphatic hydrops
10. ocular abnormalities
    A. abducens palsy: almost invariably unilateral. Often delayed 5-14 days postLP, usually recovers after 4-6 wks[157]

11. dural sinus thrombosis[158] (usually with underlying thrombophilia)

RISK OF ACUTE TONSILLAR HERNIATION FOLLOWING LUMBAR PUNCTURE

The question of when to do LP first (to save time) and when to obtain CT scan first to R/O intracranial mass (for safety) before performing an LP is controversial.

Issues

The time delay to initiating antibiotics is the most important variable in the out-come of meningitis. Time may be more crucial in community acquired meningitis, than in post-op neurosurgical meningitis.

The theoretical risk in performing an LP with an intracranial mass is that the resultant shift in pressure may precipitate tonsillar herniation.

Starting antibiotics without first having a CSF specimen risks the difficulties in managing partially treated meningitis, or a suboptimal choice of antibiotic medication.

Clinical evaluation for possible contraindication to LP is unreliable. Papilledema takes a minimum of 6 hrs to develop after the onset of increased ICP, and in most cases it requires up to 24 hrs. Therefore, its absence does not insure normal intracranial pressure. Furthermore, papilledema may be seen in conditions where there is not a contraindication to LP (e.g. idiopathic intracranial hypertension, where LP is one of the accepted treatments, *see page 713*).

The ready availability of CT scans, often within the emergency department itself, may involve a delay of only a few minutes, if qualified personnel to interpret the study are also immediately available.

Historical information

Herniation following LP was more common prior to ≈ 1950, long before CT scans were available, where the procedure was performed even when some patients had clear evidence of ↑ ICP, large bore spinal needles (12-16 gauge) were more commonly employed, and large quantities of CSF were removed for therapeutic purposes. In a 1969 report of 30 patients who deteriorated after LP[159], 73% had localizing signs (hemiparesis, anisocoria…) and 30% had papilledema. None of 5 patients with cerebral abscess deteriorated after the first of multiple LPs.

In a series of 129 patients with ↑ ICP[160], the complication rate reported was 6%; however, some of these complications were probably unrelated to LP, and

many of these patients were in extremis. In 7 series totalling 418 patients, a complication rate of 1.2% was calculated[160].

> Σ Herniation as a result of LP is consistently reported only in patients with severe non-infectious processes, often with accompanying signs of mass effect (localizing signs, papilledema…). Thus, in cases of suspected meningitis in the absence of focal findings and papilledema, if a CT scan cannot be performed and interpreted within a few minutes, the benefits of performing an LP with a needle ≤ 20 gauge and removing only a few ml of CSF and starting empiric antibiotics probably outweigh the small risk of herniation. In the unlikely event that there is acute deterioration associated with the withdrawal of a few ml of CSF, the (anecdotal) recommendation is to immediately replace the fluid through the LP needle.

HEADACHE FOLLOWING LUMBAR PUNCTURE

For characteristics of the H/A and treatment *see page 58*. Risk of post-LP H/A **(PLPHA)** is related to a number of factors including:

Factors outside the control of the physician:

1. age: ↑ in younger patients
2. sex: ↑ in females
3. prior headache history (including previous PLPHA)
4. body size: ↑ with small body mass index = weight/height^2[161]
5. pregnancy

Variables that have been shown to influence the incidence of PLPHA:

1. needle size: larger needles carry increased risk[162]
2. bevel orientation: orienting the bevel parallel to the longitudinally running fibers of the dura reduces the risk of PLPHA[163]
3. replacing the stylet prior to needle removal lowers the incidence[161]
4. the number of dural punctures (may not be totally under the physician's control)

Variables that may or may not influence the incidence of PLPHA:

1. needle type
   A. Quincke needle: bevelled edge with cutting tip (the standard LP needle). Incidence of PLPHA with 20 and 22 gauge Quincke needles: 36%[164])
   B. atraumatic needles: a number of types are available. Most are "pencil pointed" and may produce a hole with a lower incidence of transdural leak[165]. Unproven[161]

Factors found <u>not</u> to affect the incidence of PLPHA:

1. the position of the patient after LP (does not seem to prevent PLPHA, but may delay the onset of symptoms[166, 167])
2. volume of fluid removed at the time of LP
3. hydration following LP[161]

7.12.4. Lumbar drainage

Insertion of a catheter into the lumbar subarachnoid space for the purpose of draining CSF. Usually connected to a closed drainage system similar to that for an EVD. Generally used for periods of only a few days or so.

INDICATIONS

1. to reduce CSF pressure on a site of CSF leak/fistula. Example situations:
   A. dural breach during spine surgery or craniotomy (especially posterior fossa)
   B. for spontaneous CSF fistula (rare): *see page 301*
2. to reduce intracranial pressure in cases of communicating hydrocephalus: e.g. drain test for NPH (*see page 332*), or when an infected shunt has been removed
3. to reduce CSF pressure to attempt to increase perfusion of the spinal cord: e.g. during surgery for abdominal aortic aneurysm, or following spinal cord injury

CONTRAINDICATIONS

As with lumbar puncture (*see above*).

INSERTION TECHNIQUE

Positioning, entry site, and trajectory are all similar to lumbar puncture (*see above*). Instead of a spinal needle, a Tuohy needle is used. The bevel is inserted parallel to the fibers of the dura (rostro-caudal). The needle is then rotated 90° (usually pointing rostrally) and the catheter is threaded into the needle. ✖ If the catheter does not thread, the needle must be withdrawn together with the catheter - attempting to withdraw the catheter through the needle will shear off the catheter at the tip of the needle.

MANAGEMENT

The orders for the nursing staff to maintain the catheter include:

1. instructions as to how to regulate the CSF drainage. Most commonly one of:
   A. by pressure: accomplished by specifying a height of the drip chamber, usually at the level of the tragus or shoulder
   B. by withdrawing a specified amount of CSF per hour: usually 10-20 cc. This method reduces the risk of overdrainage if the dip chamber is too low
2. instructions for the exit site: usually treated as an arterial-line

COMPLICATIONS

1. infection
2. overdrainage: usually as a result of the drainage bag being too low when using the pressure drainage method described above (either from falling to the floor, or not being raised when the patient sits or stands up) or from catheter disconnection. Can cause:
   A. subdural hematoma from tearing of bridging veins from downward displacement of the brain
   B. headache
3. pneumocephalus: usually from placing the drain height below the site of a fistula, and air is drawn in through the fistula tract
   A. tension pneumocephalus: usually with a ball-valve effect at the fistula site
4. catheter pull out: frequently occurs simply as a result of patient movement in bed or with patient transfers

7.12.5. C1-2 puncture and cisternal tap

Indications

Situations where CSF specimen is required but access via LP is difficult or contraindicated (lumbar arachnoiditis, marked obesity…), or to instill contrast to demonstrate the rostral extent of a block documented by dye injected via LP. Spinal headache is less common with these procedures than with LP. C1-2 puncture is safer than cisternal tap.

✖ Contraindicated: in patient with Chiari malformation (often present in myelomeningocele) due to low lying cerebellar tonsils and medullary kink.

Normal CSF values for glucose and protein differ only slightly from CSF

obtained by lumbar puncture. Opening pressures averaged 18 cm of fluid with lateral puncture.

C1-2 PUNCTURE

AKA lateral cervical puncture. Equipment: LP tray (useful for the specimen tubes, extension tube for contrast injection under fluoroscopy, lidocaine, and spinal needle) with a standard 20 Ga spinal needle, contrast if needed (e.g. Iohexol®). It is preferred to perform the procedure under fluoro, however it has also been described without fluoroscopic guidance with a completely cooperative patient[168].

Patient position: supine in bed without a pillow, with the head straight up. Avoid any head rotation which may bring the vertebral artery **(VA)** into the needle path[169].

Place head within lateral fluoroscopy unit (since this is rarely available, a C-arm fluoro positioned horizontally may be used).

If iodinated dye is being injected for myelography, the head should be elevated to prevent contrast from running into posterior fossa; in cases with cervical spine injury, one can put the entire bed in reverse Trendelenburg.

Entry point: 1 cm caudal and 1 cm posterior (dorsal) to the tip of the mastoid process. **Needle insertion**: use a 25 Ga. needle to anesthetize the skin at the entry point. Under fluoro, advance a larger needle (e.g. 21 Ga.) towards the C1-2 interspace while injecting local anesthetic: aim for a target in the middle of the posterior third of the bony spinal canal (or, alternatively, 2-3 mm anterior to the posterior margin of the bony canal) ("**X**" in *Figure 7-32*). Leave this needle in as a marker. Insert the 20 Ga. spinal needle parallel to the marker needle. Verify the course with fluoro. If fluoro is not used, insert the spinal needle at the entry point, and advance it parallel to the plane of the bed, perpendicular to the neck[168]. If the needle penetrates deeply without encountering bone or CSF, it is most likely that the tip is too par posterior. If bone is encountered, redirect the needle in the rostrocaudal plane.

Several "pops" may be felt, and the stylet should be removed after each to check for CSF return. The subarachnoid space is ≈ 5-6 cm deep to the skin surface in most adults[170]. The needle must be supported more than with a lumbar puncture.

To inject iodinated contrast, use e.g. ≈ 5 ml of 180 mg% Iohexol® for cervical myelogram, watch dye on fluoro (should be able to see it in subarachnoid space).

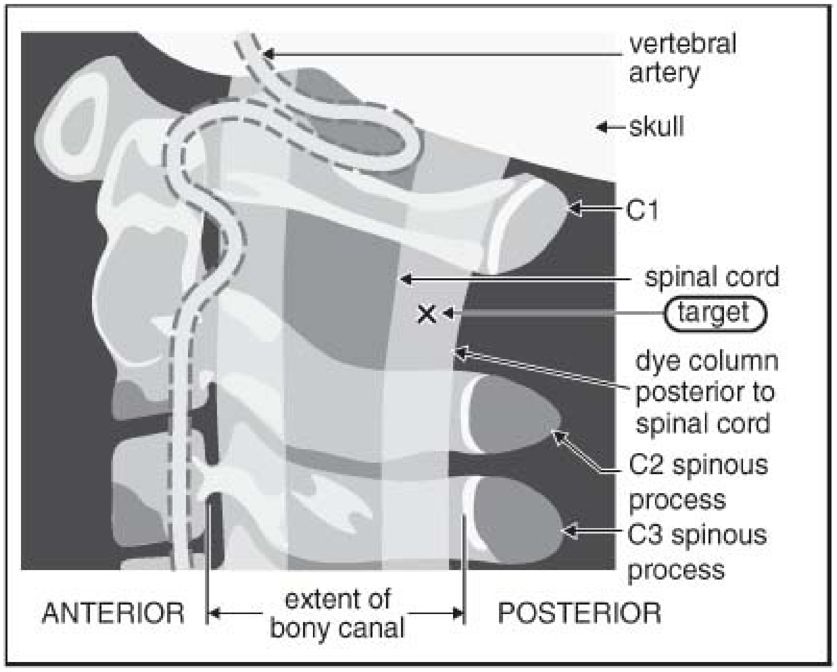

Figure 7-32 C1-2 puncture target*

* left lateral view through upper C-spine: composite diagram of a myelogram and vertebral arteriogram illustrating the relative location of the spinal cord, CSF space, and VA. Only bony landmarks will be visible with fluoroscopy

Risks

Case report of a death from subdural hematoma due to puncture of an anomalous vertebral artery[171] (found in ≈ 0.4% of population). If the VA is penetrated, the needle is withdrawn and local pressure is applied. Penetration of the upper spinal cord/lower medulla (risk of serious neurologic sequelae, even from this, is small). Herniation (as with LP) when there is increased ICP.

CISTERNAL TAP

Suboccipital access to the cisterna magna. Usually done with patient sitting, with neck slightly flexed[172]. Overlying hair should be shaved. Local anesthetic is infiltrated. A 22 gauge spinal needle is inserted exactly in the midline between the inion and the C2 spinous process, directed superiorly towards the glabella until the needle strikes the occiput or enters the cisterna magna. If the occiput is encountered, the needle is withdrawn slightly and reinserted directed slightly inferiorly, the process is repeated ("walking down the occiput") until the cisterna magna is entered (a "pop" will be felt).

The distance from the skin surface to the cisterna magna is 4-6 cm, and from

the dura to the medulla is ≈ 2.5 cm. However, due to tenting of the dura, the needle may be very close to the medulla before entering the subarachnoid space.

Risks

1. hemorrhage in the cisterna magna: may be due to perforation of a large vessel[168]
2. piercing the medulla oblongata: may cause vomiting, respiratory arrest…
3. positioning may compromise blood flow in the vertebral artery in elderly patients

7.13. CSF diversionary procedures

7.13.1. Ventricular catheterization

★ Most common insertion sites[173 (p 151-3)]:

1. **occipital-parietal** region: commonly used for CSF shunt
   A. entry site: a number of means have been described, including:
      1. **Frazier burr hole**: placed prophylactically before p-fossa crani for emergency ventriculostomy in event of post-op swelling. Location: 3-4 cm from midline, 6-7 cm above inion[40 (p 520)] (caution: an error in locating the inion could put the catheter in an undesirable location if this method alone is used)
      2. **parietal boss**: flat portion of parietal bone
      3. follow point from mid-pupillary line parallel to sagittal suture until it intersects line extending posteriorly from the top of the pinna
      4. ≈ 3 cm above and ≈ 3 cm posterior to top of pinna
   B. trajectory: insert the catheter parallel to skull base:
      1. initially aim for middle of forehead
      2. if this fails, aim for ipsilateral medial canthus
   C. insertion length: ideally, the tip should be just anterior to the foramen of Monro in the frontal horn[174]. Ventriculoscopic guidance (if available) increases the accuracy to a significant degree. In the absence of this:
      1. intracranial length should be ≈ two thirds of the length of the skull (this is short enough to prevent penetration of frontal brain

parenchyma, but long enough to take tip beyond the foramen of Monro to prevent catheter from ending up in the temporal horn where choroid plexus increases the chance of obstruction)
    2. in adults without macrocrania the inserted length is usually ≈ 12 cm when the burr hole is in line with the axis of the lateral ventricle[175] (lengths > 12 cm are rarely required). In hydrocephalic infants usually ≈ 7-8 cm is required
    3. use the stylet for the initial ≈ 6 cm of insertion, then remove it and insert the remaining length (keeps the catheter straight during penetration of occipital parenchyma and prevents the tip from dropping into the temporal horn where there is choroid plexus, also the temporal horn may collapse and occlude the catheter when the HCP is resolved)
2. **Keen's point** (posterior parietal): (placement in trigone) 2.5-3 cm posterior and 2.5-3 cm superior to pinna (was the usual site of occurrence of cerebral abscesses arising from otitis media, and was often used to tap these)
3. **Dandy's point**: 2 cm from midline, 3 cm above inion (may be more prone to damage visual pathways than above)

★ 4. **Kocher's point** (coronal): places catheter in frontal horn. The right side is usually used. Commonly employed for ICP monitors
   A. entry site: 2-3 cm from midline which is approximately the mid-pupillary line with forward gaze, 1 cm anterior to coronal suture (to avoid motor strip)
   B. trajectory: direct catheter perpendicular to surface of brain, which can be approximated by aiming in coronal plane towards medial canthus of ipsilateral eye and in AP plane towards EAM
   C. insertion length: advance catheter with stylet until CSF is obtained (should be < 5-7 cm depth; this may be 3-4 cm with markedly dilated ventricles). Advance catheter without stylet 1 cm deeper. ✖ CAUTION: if CSF is not obtained until very long insertion length (e.g. ≥8 cm) the tip is probably in a cistern (e.g. prepontine cistern) which is undesirable

7.13.2. Ventriculostomy/ICP monitor

AKA intraventricular catheter **(IVC)** or external ventricular drainage **(EVD)**.

Insertion technique

Unless contraindicated (e.g. right ventricular bleed), the right (non-dominant) side is preferred. Clip the hair around the planned incision site and the exit site for the tunneled catheter (avoid shaving which degrades the skin's barrier function against infection). Five minute Betadine prep.

Site: approximately Kocher's point (*see above*). To avoid motor strip, enter 1-2 cm anterior to coronal suture (estimated position of coronal suture: follow line up midway between lateral canthus and EAM), and to avoid the sagittal sinus, 2-3 cm lateral to mid-line (2 fingerbreadths or ≈ 3 cm is commonly employed as an approximation). Incision oriented in sagittal plane (in case it needs to be incorporated in flap); elevate periosteum; place self-retaining retractor; make twist drill hole. Bone-wax edges to stop bone bleeding; cauterize dura with bipolar coagulator; incise dura in cruciate fashion with #11 scalpel blade; cauterize incised dural edges and then pia/arachnoid with bipolar.

For ventriculostomy: insert catheter perpendicular to brain surface[176] to a depth of 5-7 cm (most catheters are marked at 5 and 10 cm). With any ventricular enlargement, CSF should flow at least by 3-4 cm depth (with normal ventricles, this may be 4-5 cm). If no CSF is encountered here and the catheter is passed further until CSF is obtained, it is unlikely to be due to catheterization of frontal horn of lateral ventricle (in this case, at ≈ 9-11 cm the tip will often be in the pre-pontine cistern, a subarachnoid space, which is undesirable). If unsuccessful after a maximum of three attempted passes, then place a subarachnoid bolt or intraparenchymal monitor.

For (Richmond) subarachnoid bolt: screw in until tip is flush with inner table.

Removal

Patients receiving anticoagulants need to have normal coagulation and platelet function before discontinuing the catheter to reduce the risk of intracranial hemorrhage. For heparin and LMW heparin, stop the drug 24 hours prior to discontinuing the drain.

Sump drainage"

The tip of a 25 gauge butterfly may be bent at a 90° angle, and inserted into a sub-cutaneous reservoir for prolonged ventricular drainage[177]. In one series OF 34 patients, this was used for prolonged periods (up to 44 days) with acceptably low infection rate[178]. The use of a one-way valve, continuous antibiotics (ampicillin and cloxacillin) and meticulous technique was credited for the lack

of infection.

7.13.3. Ventricular shunts

Booking the case - ventricular shunt

Also see defaults & disclaimers (*page v*).

1. position: supine with shoulder roll
2. implants: need to specify shunt manufacturer and valve type (e.g. programmable, low profile…) desired
3. equipment:
   A. C-arm for ventriculo-atrial shunts
   B. endoscopic display (e.g. if NeuroPen is used)
   C. image guided navigation system (infrequently used)
4. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery to insert a permanent drainage tube from the brain to the abdomen, outside of the lungs, vein near the heart (as appropriate) to drain excess cerebrospinal fluid
   B. alternatives: nonsurgical management (rarely effective for hydrocephalus), third ventriculostomy (for certain cases)
   C. complications: infection, suboptimal position which might require re-operation, failure to relieve hydrocephalus/symptoms, subdural hematoma, bleeding in the brain, shunts are mechanical devices and will eventually fail (break, block up, move…) and need repair/replacement (sometimes sooner rather than later). Abdominal shunts: risk of bowel injury (which could require further surgery)

Ventricular catheter

Occipital burr hole is used in most cases for insertion site of ventricular catheter (see *Ventricular catheterization* *page 207* for technique). Some prefer a frontal burr hole (Kocher's point) citing a lower incidence of failure from choroid plexus occlusion (this is controversial). The use of flanged catheters (designed to keep choroid plexus away from catheter holes) is discouraged because these actually have a higher incidence of choroid plexus occlusion and these catheters can become so entangled that removal is impossible without

significant risk of hemorrhage.

An inverted "J" shaped incision is used to keep hardware from lying directly under the skin incision (minimizes risk of skin breakdown and also creates additional barrier to infection of subjacent hardware). CSF should be sent for culture at the time of insertion since it has been estimated that in ≈ 3% of patients the CSF is already infected. 4 mg of preservative-free gentamicin may instilled into the ventricular catheter by the technique of **barbotage**, (a technique to administer a drug while reducing the amount of drug lost in the dead space of the catheter: a portion of the antibiotic solution is injected into the CSF, then a lesser amount of CSF is aspirated, a second portion is then injected and the process is repeated until all of the medication is administered).

If you think the catheter is in the ventricle, but you don't get CSF flow, it may be due to low pressure, you can compress the jugular veins or lower the head of the bed to try and induce CSF flow.

Connectors

If a connector must be used near the clavicle, placing it below the clavicle increases the risk of disconnection vs. placing the connector above the clavicle.

DISTAL CATHETER PLACEMENT

All things being equal, the general order of preference for distal catheter placement:

1. peritoneal cavity: *see below*
2. pleural space: (not for age ≤ 7 years - *see page 316*). For technique, *see below*
3. right atrium or superior vena cava: *see page 210*
4. less frequently used distal shunt sites
   A. gall bladder
   B. internal jugular vein (with the catheter pointing "upstream")
   C. superior sagittal sinus

VENTRICULOPERITONEAL SHUNT

Peritoneal catheter

For small children, use at least 30 cm length of intraperitoneal tubing to

allow for continued growth (120 cm total length of peritoneal tubing was associated with a lower revision rate for growth without significant increase in other complications[179]). A silver clip is placed at the point where the catheter enters the peritoneum so that the amount of residual intraperitoneal catheter can be determined on later films (more important in growing children).

Distal slits on the peritoneal catheter may increase the risk of distal obstruction[180], and some authors recommend that they be trimmed off. Wire reinforced catheters should not be used because of excessively high rate of viscus perforation, and this tubing was designed to prevent kinking which is not a problem with modern shunts.

Open technique: A vertical incision lateral and superior to the umbilicus is one of several choices. The following layers should be identified as they are traversed to avoid confusing preperitoneal fat with omentum and erroneously placing the tip in the preperitoneal space:

1. subcutaneous fat
2. anterior sheath of the abdominis rectus muscle (anterior rectus sheath)
3. abdominis rectus muscle fibers: should be split longitudinally
4. posterior rectus sheath
5. preperitoneal fat (may be very well developed in a few individuals, but is essentially nonexistent in most)
6. peritoneum (usually closely adherent to the posterior rectus sheath)

Trocar technique:

1. place a Foley catheter to decompress the bladder
2. 1 cm skin incision above and lateral to the umbilicus
3. pull abdominal skin anteriorly (away from patient)
4. insert trocar aiming toward the ipsilateral iliac crest
5. feel 2 “pops” of penetration: 1 = anterior rectus sheath, 2 = posterior rectus sheath/peritoneum
6. peritoneal catheter should feed easily through trocar

VP SHUNT, POST-OP ORDERS (ADULT)

1. flat in bed (to avoid overshunting and possible subdural hematoma) with gradual mobilization
2. if peritoneal end is new or revised, do not feed until bowel sounds resume (usually at least 24 hrs, due to ileus from manipulation of peritoneum)
3. shunt series (AP & lateral skull, and chest/abdominal x-ray) as baseline for

future comparison (some surgeons obtain these films immediately post-op in case some immediate revision is indicated, e.g. ventricular catheter tip in temporal horn)

VENTRICULOPLEURAL SHUNT INSERTION[181]

Not for age ≤ 7 years (*see* *page 316*). A 3 cm horizontal incision is made just below the level of the breast either in the midclavicular line or in the anterior axillary line. Divide the subcutaneous tissue, deep fascia, and pectoralis muscle. The external and internal intercostal muscles are divided along the superior margin of the inferior of the two ribs exposed (to avoid the neurovascular bundle running along the inferior margin of each rib). A self retaining retractor between the ribs aids the exposure. The parietal pleura is visualized with the visceral pleura sliding underneath with each respiration. The pleura is not opened until the catheter is brought out subcutaneously at this incision. Have the anesthesiologist hold respirations, and nick the parietal pleura (or use a blunt-tip hemostat to pop through) to admit the catheter. Allow the lung to drop away and insert 20-40 cm of tubing into the pleural cavity. If the pleural opening is lax around the catheter, it can be snugged with a 4-0 absorbable suture. Have the anesthesiologist provide a valsalva maneuver before cinching down the pleural suture, and again before closing the deep muscle layer. A chest tube is usually not required. A maneuver that may sometimes be helpful is to place a red-rubber catheter next to the shunt tube at the same time (to permit the escape of air from the pleural space). Begin closing, but prior to placing the last deep suture, have the anesthesiologist perform a valsalva maneuver and pull the red-rubber catheter and close the last stitch (the red tubber catheter permits air to exit the pleural space). Check a CXR in the recovery room for significant pneumothorax.

VENTRICULO-ATRIAL SHUNT INSERTION

Open method

The common facial vein **(CFV)** is located by making a diagonal cervical incision across the anterior border of the sternocleidomastoid at or just below the level of the angle of the mandible (the CFV may be as far as ≈ 2 cm below this point). The platysma is divided, and the CFV is located as it joins the internal jugular vein **(IJV)** at the level of the hyoid bone. The CFV is cannulated with the atrial tubing, and is secured with a snug ligature close to the junction with the IJV. If the CFV is not suitable, a purse string suture is placed directly in the IJV,

and the IJV is then opened in the center of the purse string and cannulated.

Percutaneous method

May be utilized in adults (and possibly peds). The IJV is catheterized using the Seldinger technique[182] with a guide-wire and needle through a stab wound at the anterior margin of the SCM. Fluoroscopy is used to place the tip of the wire at the desired location (*see below*). A No. 13 French peel-away introducer and dilator are then inserted over the wire, which is then bent at the skin edge and withdrawn[183] (for a pediatric case: may use a No. 7 French introducer with a 1.5 mm O.D. lumboperitoneal catheter for the distal atrial catheter). The atrial catheter is cut to the length of the wire distal to the bend, and the catheter is then threaded into the introducer. The position of the catheter tip should again be confirmed (e.g. with radioopaque contrast under fluoroscopy). A short skin incision is then made starting at the point where the catheter penetrates the skin to permit subcutaneous tunnelling of the tubing.

Location of distal tip

Placement pointer: if the catheter repeatedly goes down the wrong vessel (e.g. the subclavian vein), a “J” guidewire may help. Also, rotating the head to a more neutral position sometimes works.

The ideal location of the distal tip is in the superior vena cava **(SVC)** near the right atrium so that the turbulent blood flow will reduce the risk of thrombus formation. The tip may enter the right atrium, but must not penetrate the tricuspid valve. A number of methods for optimal placement of the distal shunt tip may be employed, and include:

1. using an intraoperative chest x-ray to locate the tip between the level of T6-T8 vertebra in an adult. In a growing child, initially insert to ≈ T10 level. This method is subject to error due to malalignment of the x-ray beam (parallax error)
2. locating the tip near the level described above, then inject iodinated contrast (e.g. 20 ml of Omnipaque 180 (iohexol), *see page 122*) under intraoperative fluoroscopy to locate the tip in SVC
3. fill the catheter with normal or 3% saline and use the catheter as an EKG electrode. The P-wave changes from a downward to a biphasic morphology as the tip enters the atrium. A sharp upward deflection occurs as the tricuspid valve is approached[184]. Some recommend advancing the tip to maximal P-wave amplitude and then backing off a centimeter or two

4. fill the catheter with heparinized saline (1-5 U per cc NS) and measure the pressure as the tip is advanced[185], leave tip just short of where atrial pressure tracing occurs
5. utilizing intraoperative echocardiography[186]

A growing patient is followed with annual CXRs. When the catheter tip is above ≈ T4, the catheter must be lengthened or converted to a VP shunt.

7.13.4. Ventricular access device

An indwelling ventricular catheter connected to a reservoir that is situated under the scalp for the purpose of chronic access to the intrathecal space (usually the ventricular system), or some other compartment. Sometimes referred to as an Ommaya® reservoir.

INDICATIONS

Indications for insertion:

1. administration of intrathecal **(IT)** antineoplastic chemotherapy:
   A. for CNS neoplasms, including: carcinomatous meningitis, CNS lymphoma or leukemia (*see page 675*)
   B. IT chemotherapy is often used for the following even in the *absence* of CNS involvement because of the high relapse rate in the CNS: acute lymphoblastic leukemia, lymphoblastic lymphoma, Burkitt's lymphoma
2. administration of intrathecal antibiotic for chronic meningitis
3. chronic removal of CSF from infants with intraventricular hemorrhage
4. for fluid aspiration from a chronic tumor cyst that is resistant to therapy (radiation or surgery)

BOOKING THE CASE - VENTRICULAR ACCESS DEVICE

Also see defaults & disclaimers (*page v*).

1. position: supine
2. equipment
   A. endoscopic display (e.g. if NeuroPen is used)
   B. C-arm (optional) to verify position of ventricular catheter

C. image guided navigation system (if used)
3. implants: need to specify reservoir manufacturer
4. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery to insert a tube into the fluid space within the brain (ventricle) which is connected to a port under the skin so that fluids can be removed or injected (usually medication)
   B. alternatives: sometimes fluid can be removed and medication can be injected using a lumbar puncture (spinal tap). The effectiveness of this may not be the same as the operation being discussed here
   C. complications: infection, suboptimal position which might require re-operation, subdural hematoma, bleeding in the brain, this is a mechanical device and may eventually fail (break, block up…) and need repair/replacement

TECHNIQUE OF INSERTION[187]

Preferably placed in the right frontal region, unless indicated otherwise (e.g. for tumor cyst). Usually placed under endotracheal general anesthesia, although local anesthesia occasionally may be used (e.g. for patients too ill to tolerate general anesthesia).

Patient position: supine, head midline, neck flexed 5°.

Incision: inverted "U", slightly larger than the reservoir (the original Ommaya® reservoir is 3.4 cm diameter), with the center over the coronal suture approximately 3 cm from midline (roughly centered near Kocher's point, *see page 207*). A circle of pericranium of diameter equal to that of the reservoir is excised and saved. Alternatively, the pericranium may be flapped separately in the opposite direction (i.e. a right-side-up "U"), and closed over the reservoir to help secure it in position.

Make a burr hole over the coronal suture 3 cm off midline. A cruciate incision in the dura is made large enough to visualize the cortical surface, minimal cortical bipolar coagulation is used, and a pial/cortical incision is made to avoid surface vessels.

One may inject 15-20 cc of filtered air into the ventricles with a ventricular needle prior to the catheter insertion to guide the tip of the catheter with intraoperative lateral skull x-rays (intraoperative pneumoencephalogram). The trajectory is towards a point intersecting a plane 2 cm anterior to the EAM aiming minimally towards the midline (1-2°). Alternatively, one may aim perpendicular to the surface of the skull[176]. A total length of **≈ 7.25 cm** of catheter is fixed to the base of the reservoir which allows the catheter to lie on

the floor of the anterior horn of the lateral ventricle in most adults. This location can be verified with intraoperative pneumoencephalography[187] or with ventriculoscopic techniques.

The excised pericranium is placed over the dura, and the reservoir is sutured to the pericranium. Note: the dome of the original Ommaya® reservoir has a low resistance, and may be easily collapsed if too much tension is placed on the overlying scalp. If early use of the reservoir is desired (i.e. within 48 hrs post-op), the skin closure should be performed with a running nonabsorbable suture (e.g. nylon) and coated with collodion, and the surgical site can then be left without a gauze dressing for easier access to the reservoir. A skin tattoo can be created over the center of the reservoir (to assist in localizing the reservoir for injection) using India ink and a pricking the skin with a sterile needle.

RESERVOIR PUNCTURE

The scalp is prepped with antimicrobial scrub, and using sterile technique, a 25 gauge or smaller butterfly needle is introduced at an oblique angle, preferably with a non-coring needle. The original (Ommaya®) reservoir has firm plastic bottom surface which can be penetrated if too much force is applied.

7.13.5. Third ventriculostomy

See page 315 for indications and complications.

Older techniques include a subfrontal approach, opening the chiasmatic and lamina terminalis cisterns, and making a 5-10 mm opening in the lamina terminalis. Stereotactic third ventriculostomy (using contrast ventriculography[188] or CT guided) has also been described. Current technique consists of fenestrating the floor of the third ventricle using the ventriculoscope.

Ventriculoscopic technique

1. equipment: requires a rigid endoscope (does not work well with flexible)
2. image guided stereotactic technology helps immensely with the trajectory, but once you've entered the third ventricle, you must navigate by visual landmarks and cannot rely on image guidance because of the limitations of the accuracy
3. burr hole: 2-3 cm lateral to the midline just anterior to the coronal suture
4. pass through the foramen of Monro
5. the floor of the third ventricle is inspected and must be thin enough and

translucent enough to permit visualization of the basilar artery and mammillary bodies. If these structures cannot be visualized then the procedure should be aborted

6. the location of the opening is chosen:
   A. in the midline
   B. in the region of the tuber cinereum (prominence of the base of the hypothalamus, extending ventrally into the infundibulum and pituitary stalk)
   C. posterior to the infundibular recess
   D. anterior to the mammillary bodies
   E. anterior to the tip of the basilar artery
7. an effective technique consists of “rubbing through” the floor of the third ventricle either with a probe or with the tip of the scope itself. Alternatively, electrocautery may be used to thin down the lamina. ✖ Do not use laser due to possibility of injury to basilar artery[189]!
8. the opening can be enlarged with the use of a Fogarty catheter if needed. The balloon is inflated distal to the opening in the floor and is then withdrawn through the opening
9. the opening does not need to be large (unlike e.g. fenestrating an arachnoid cyst): ≈ 4-5 mm is usually adequate[190, 191]
10. after penetrating through the floor of the third ventricle, make certain that you can see vessels (sometimes the arachnoid is not perforated, or there is a second membrane or webs of membranes that need to be lysed)

Complications

(also, *see page 315*)

1. injury/perforation of the basilar artery
2. injury to the pituitary stalk or pituitary gland

7.13.6. LP shunt placement

TECHNIQUE OF INSERTION[192]

1. position: lateral decubitus position, both knees flexed (right side up preferred)
2. prep back, flank and abdomen

3. 1 cm skin incision over L4-5 or L5-S1 (in obese patients, use larger skin incision carried down to fascia overlying spinous processes. This may also be superficially incised between spinous processes to aid insertion)
4. tilt table to 30° reverse-Trendelenburg to expand lumbar subarachnoid space
5. insert 14 gauge Tuohy needle into subarachnoid space, with opening directed rostrally (caudal placement also acceptable). Confirm placement by CSF flow
6. remove trocar, insert shunt tubing such that **≤ 8 cm** of catheter (for L4-5 insertion) lies within spinal canal (minimizes conus medullaris irritation)
7. needle then withdrawn over catheter
8. make flank incision, pass tunneler from flank to back incision. Feed catheter from back to flank. Withdraw tunneler over catheter
9. abdominal placement:
    A. open: incision made through peritoneum. Catgut (or other absorbable suture) purse-string placed in peritoneal opening
    B. trocar
10. pass tunneler from abdominal incision to flank incision. Feed catheter from flank to abdomen. Withdraw tunneler over catheter
11. verify CSF flow. Place catheter inside peritoneum. For open technique: cinch purse-string snugly, but loose enough to allow catheter to slide with gentle pushing
12. snug fitting retaining sleeve placed around catheter at all three incisions, and secured to subcutaneous tissue with non-absorbable suture

LUMBOPERITONEAL (LP) SHUNT EVALUATION

When problems develop, evaluation of function may be more difficult than with VP shunt. Evaluation may include:

1. **abdominal x-rays**: AP & lateral x-rays can rule out breakage or migration of a shunt component
2. **noncontrast brain CT**: can rule-out complication such as subdural hematoma
3. **LP**: perform LP just above or below level of lumbar catheter. The pressure may be 0 or negative, and it may be necessary to aspirate CSF to confirm placement
    A. can give indirect evidence of shunt function by measuring the CSF pressure, which should be low if the shunt is working (only helpful in

cases where the shunt was placed for elevated CSF pressure, e.g. pseudotumor cerebri; not helpful in NPH).

B. "shunt-o-gram": inject contrast into subarachnoid space through LP needle

1. radionuclide: inject radio-isotope via LP and look for subsequent tracer activity in peritoneal cavity (*see page 324*)
2. with water-soluble contrast[193]: inject 10 ml of iohexol and monitor the flow of contrast fluoroscopically as the patient is brought vertical. Coughing or valsalva maneuver will accelerate the flow of contrast

4. **shunt tap**: if an antechamber has been installed, it is accessed after cleaning the skin with antiseptic using a 22 Ga. or smaller needle placed perpendicular to the dome to prevent leakage. If there is no access chamber, it is sometimes possible to tap the tubing itself with a 27 gauge butterfly needle

7.14. Sural nerve biopsy

Although a number of peripheral nerves may be biopsied, the sural nerve fulfills the criteria of being well studied, expendable with minimal deficit, easily accessible, and often involved in the pathologic process in question.

Indications

Nerve biopsy plays a small role in diagnosing peripheral neuropathies, but may be very accurate for vasculitis, amyloidosis, Hansen's disease, metachromatic and globoid leukodystrophy, neoplastic infiltration of peripheral nerve, and relapsing polyneuritis[194 (p 316)]. May help distinguish the two types of Charcot-Marie-Tooth syndrome. May show demyelination in diabetic amyotrophy (*see page 796*).

Anatomy

The sural nerve is formed by the merging of the distal portion of the medial sural cutaneous nerve (one of the terminal branches of the tibial nerve) and the anastomotic ramus of the common peroneal nerve. It is entirely sensory except for some unmyelinated autonomic fibers. It supplies cutaneous sensation to the posterolateral third of the leg, the lateral heel and foot, and the little toe. At the

level of the ankle it lies between the Achilles tendon and the lateral malleolus. This location is constant, superficial, and relatively protected from external trauma which might otherwise confuse the analysis.

Technique

Modified technique[195 (p 771-2)]. Usually done under local anesthesia with sedation. Position: patient prone or three-quarters prone, pillow between the legs. The leg to be biopsied is uppermost and is flexed 90° at the knee to relax tension on the nerve, the ankle is slightly everted. Compressing the calf distends the lesser saphenous vein **(LSV)** at the lateral malleolus **(LM)**, which (when visible) reliably locates the sural nerve usually deep and anterior to the vein. A sterile Penrose drain is useful as a temporary tourniquet for this purpose during surgery.

After prepping, drape the limb with a sterile stockinette or similar drape, infiltrate local anesthetic subcutaneously just posterior to the LM and proximally, paralleling the Achilles tendon for ≈ 10 cm. A 7-10 cm incision is made overlying the course of the LSV beginning usually just posterior to and ≈ 1 cm proximal to the LM. The vein can be seen through the translucent Scarpa's fascia. The fascia is incised over the vein which is gently retracted to reveal the nerve usually deep to the vein. A common pitfall is to go too deep, the nerve is fairly superficial; it is not necessary to go through the thick fascia. If at any time you see tendons to the toes, you have gone too deep.

To differentiate the sural nerve from the LSV (which may resemble the nerve in some cases): the nerve has many branches at acute angles especially proximal to the LM, vs. the vein which has right angle branches. A nerve stimulator and/or frozen section may also be helpful (frozen section just to verify that the biopsied structure is a nerve) and one or the other is *highly recommended* to avoid potentially embarrassing explanations and the possible need to repeat the procedure.

After exposing at least 3-5 cm of the nerve, anesthetize the proximal portion with 0.5% lidocaine using a 27 Ga. needle and cut it sharply just distal to the infiltration site (note: sometimes a biopsy of only a portion of the nerve's fascicles may suffice: this is accomplished by opening the epineurium for the length of the exposure and teasing out a fascicle with minimal branching). Cut the nerve with slight tension on it to allow the ends to retract deep to the skin incision to prevent the formation of a scar neuroma. Some pathologists request that the proximal end of the nerve be marked, e.g. with a suture.

An elastic pressure dressing is applied after closure.

If it is desired to obtain a biopsy of the sural nerve higher up for comparison, it may be accessed in the mid upper calf between the heads of the gastrocnemius muscle. Here it may be as deep as ≈ 2 cm. Gently tugging on the exposed nerve in the ankle may help in localization.

Post op care: Pressure dressing should be worn for protection for two weeks. The patient is allowed to walk but should restrict their activity for 2-3 days. If nonabsorbable sutures are used instead of subcuticular closure, they should be left in place 10-14 days.

NERVE HANDLING

For light microscopy which suffices in most cases, immerse the nerve in formalin. For electron microscopy, glutaraldehyde is used. For biochemical and immunofluorescence studies, use rapid freezing.

RISKS OF PROCEDURE

1. sensory loss in the sural nerve distribution is *expected*, but often does not persist for more than several weeks (unless the underlying disease process prevents this)
2. problems with wound healing: the ankle is a notorious region for poor circulation and the loss of sensation (from the disease or biopsy) may render the area subject to repeated trauma without the patient being aware. Furthermore, many patients with an undiagnosed systemic disease requiring a sural nerve biopsy will have poor wound healing (a significant number are also diabetic)
3. failure to make a diagnosis: although biopsy may be able to exclude some contingencies, it often does not make a specific diagnosis

7.15. Nerve blocks

Also see *Occipital nerve block*, page 805.

7.15.1. Stellate ganglion block

✖ Do not perform stellate ganglion block bilaterally (can cause bilateral laryngeal paralysis → respiratory compromise). Stellate ganglion is actually

closer to C7 than C6, but risks at C7 are much higher (closer to pleura → pneumothorax, vertebral artery → arterial injection → seizures and/or hematoma, recurrent laryngeal nerve → unilateral vocal cord paralysis → hoarseness (common), brachial plexus → UE weakness). Other complications: intradural injection → spinal anesthesia, phrenic nerve block.

Technique

Patient supine; interscapular roll; head tilted backward, mouth slightly open to relax strap muscles. Displace SCM and carotid sheath laterally, insert 1.5 inch 22 Ga. needle to contact **Chassaignac's tubercle** (anterior tubercle of transverse process of C6) AKA **carotid tubercle** (the most prominent in the C-spine) usually at the level of the cricoid cartilage, approximately 1.5-2 inches above clavicle.

Withdraw needle 1-2 mm and aspirate (do not inject intravascularly). Inject small test dose, then full 10 ml of 0.5% bipuvicaine (Marcaine®) or 20 ml of 1% lidocaine. Remove needle and elevate patient's head on pillow to facilitate spread.

Verify block by Horner's syndrome, and anhidrosis and increased warmth of ipsilateral hand.

7.15.2. Lumbar sympathetic block

Technique

Patient prone on fluoro table. Use local anesthetic to allow insertion of 20-22 gauge spinal needles (10 to 12.5 cm long) at L2, L3 and L4 levels. Needle inserted 4.5-5 cm lateral to spinous process until transverse process contacted, then redirected caudally and inserted to a depth 3.5-4 cm deeper than transverse process. Final needle tip position should be just anterolateral to vertebral bodies. At each level, instill ≈ 8 ml of 1% lidocaine local after verifying that nothing can be aspirated.

Keep patient on bed rest for several hours, then ambulate with assist; watch for orthostatic hypotension due to vascular pooling in blocked lower extremity.

7.15.3. Intercostal nerve block

Indications

1. postthoracotomy pain
2. intercostal neuralgia
3. postherpetic neuralgia
4. pain from rib fractures

Procedure

In order to obtain good anesthesia, the following should be noted:

1. a good site for injection is in the posterior axillary line **(PAL)** because
   A. this is proximal to the origin of the lateral cutaneous nerve (which originates ≈ in the anterior axillary line)
   B. this avoids the scapula for nerves above ≈ T7
   C. this reduces the risk of pneumothorax from injecting closer to the spine (the latter requires a longer needle path and there is increased difficulty palpating landmarks)
2. due to overlap, at least 3 intercostal nerves usually need to be blocked to achieve at least some area of anesthesia; it is usually necessary to block 1-2 intercostal nerves both above and below the affected dermatome
3. the intercostal nerves lie on the undersurface of the corresponding rib in close proximity to the pleura; the order of structures from top down is: rib, vein, artery, nerve

Technique

1. after raising a skin wheal at the desired level in the PAL, insert a 22 Ga. or smaller needle directly against the rib
2. walk the needle down the rib millimeter by millimeter until the needle just slips under the rib; to avoid pleural puncture, do not advance the needle more than one-eighth inch deep to the anterior surface of the rib
3. aspirate to be certain that there is no air (from lung penetration) or blood (from entering the intercostal artery or vein)
4. if no air or blood returns, inject 3-5 ml of local anesthetic
5. if there is any question about lung penetration, obtain a portable CXR to R/O pneumothorax

7.16. References

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8. Developmental anomalies

8.1. Arachnoid cysts

8.1.1. Arachnoid cysts, intracranial

Key concepts:

- a congenital abnormality, most common in middle fossa, cerebellopontine angle **(CPA)**, suprasellar region, and posterior fossa
- usually an incidental finding
- imaging often shows remodeling of bone; imaging characteristics exactly mimic CSF on CT or MRI in most cases
- recommendation for incidentally discovered arachnoid cyst in adults: a single follow-up imaging study in 6-8 months is usually adequate to rule-out any increase in size. Subsequent studies only if concerning symptoms develop

AKA **leptomeningeal cysts**, distinct from *posttraumatic* leptomeningeal cysts (AKA growing skull fractures, *see page 892*), and unrelated to infection. Arachnoid cysts **(AC)** are congenital lesions that arise during development from splitting of arachnoid membrane (thus they are technically *intra-arachnoid* cysts) and contain fluid that is usually identical to CSF. They do not communicate with the ventricles or subarachnoid space. May be unloculated or may have septations. Typically lined with meningothelial cells positive for epithelial membrane antigen **(EMA)** and negative for carcinoembryonic antigen (CEA). AC may also occur in the spinal canal.

"Temporal lobe agenesis syndrome" is a label that had been used to describe the findings with middle cranial fossa ACs. This term is now obsolete since brain volumes on each side are actually the same[1], bone expansion and shift of brain matter account for the parenchyma that appears to be replaced by the AC.

Two types of histological findings[2]:

1. “simple arachnoid cysts”: arachnoid lining with cells that appear to be capable of active CSF secretion. Middle fossa cysts seem to be exclusively of this type
2. cysts with more complex lining which may also contain neuroglia, ependyma, and other tissue types

EPIDEMIOLOGY OF INTRACRANIAL ARACHNOID CYSTS

Incidence: 5 per 1000 in autopsy series. Comprise ≈ 1% of intracranial masses.

Male:female ratio is 4:1. More common on the left side.

Bilateral arachnoid cysts may occur in Hurler syndrome (a mucopolysaccharidosis).

Table 8-1 Distribution of arachnoid cysts[6]

Location	%
sylvian fissure	49%
CPA	11%
supracollicular	10%
vermian	9%
sellar & suprasellar	9%
interhemispheric	5%
cerebral convexity	4%
clival	3%

DISTRIBUTION

Almost all occur in relation to an arachnoid cistern (exception: intrasellar, the only one that is extradural), *see Table 8-1*.

Epidermoid cysts in the cerebellopontine angle **(CPA)** may mimic an arachnoid cyst, but are high signal on DWI MRI (*see page 690*).

For the differential diagnosis of midline posterior fossa arachnoid cysts, (*see page 240*).

PRESENTATION

Most ACs are asymptomatic. Those that become symptomatic usually do so in early childhood[3]. The presentation varies with location of the cyst, and oftentimes appear mild considering the large size of some.

Typical presentations are shown in *Table 8-2*[3] and include:

1. symptoms of intracranial hypertension (elevated ICP): H/A, N/V, lethargy
2. seizures
3. sudden deterioration:
   A. due to hemorrhage (into cyst or subdural compartment): middle fossa cysts are notorious for hemorrhage due to tearing of bridging veins. Some sports organizations do not allow participation in contact sports for these patients
   B. due to rupture of the cyst
4. as a focal protrusion of the skull
5. with focal signs/symptoms of a space occupying lesion
6. incidental finding discovered during evaluation for unrelated condition
7. suprasellar cysts may additionally present with[4]:
   A. hydrocephalus (probably due to compression of the third ventricle)
   B. endocrine symptoms: occurs in up to 60%. Includes precocious puberty
   C. head bobbing (the so-called “bobble-head doll syndrome”[5]): considered suggestive of suprasellar cysts, but occurs in as few as 10%
   D. visual impairment

Table 8-2 Typical presentations of arachnoid cysts

Middle fossa cysts	Suprasellar cysts with hydrocephalus	Diffuse supra- or infratentorial cysts with hydrocephalus
seizures headache hemiparesis	intracranial hypertension craniomegaly developmental delay visual loss precocious puberty bobble-head doll syndrome	intracranial hypertension craniomegaly developmental delay

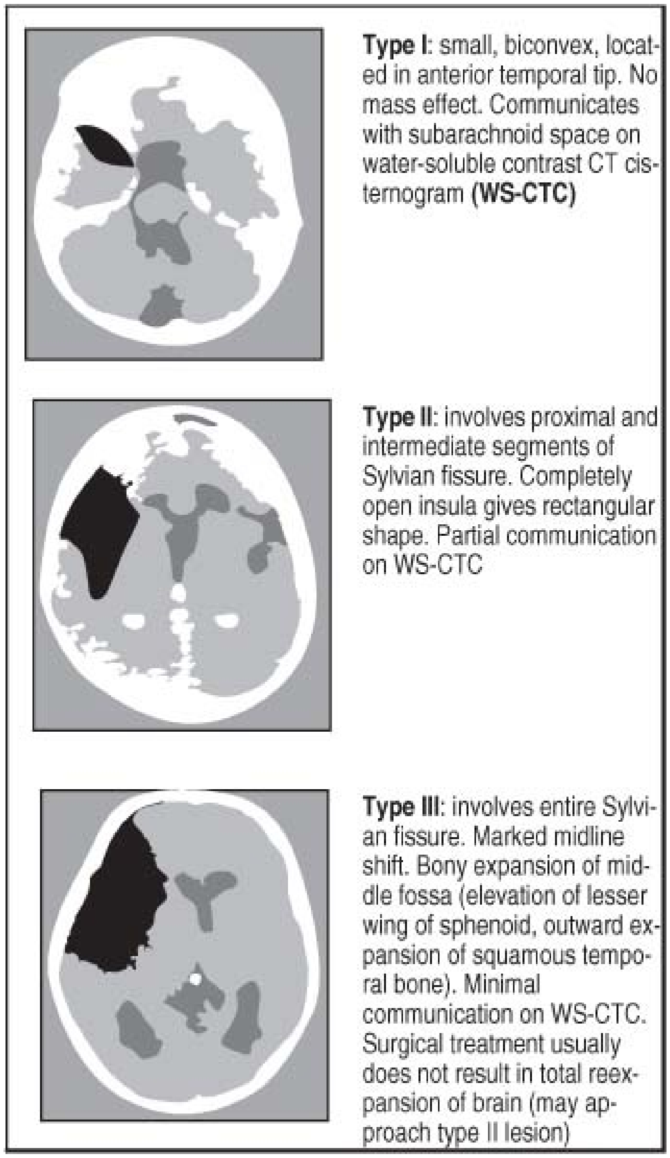

Figure 8-1 CT Classification of Sylvian fissure cysts[7]

EVALUATION

Routine evaluation with CT or MRI is usually satisfactory. Further evaluation with CSF contrast or flow studies (cisternograms, ventriculograms…) are only occasionally necessary for the diagnosis of midline suprasellar and posterior fossa lesions[3] (for Differential diagnosis, *see Intracranial cysts*, page 1217). See *Figure 8-1* for classification for middle fossa cysts.

CT SCAN

Smooth bordered non-calcified extraparenchymal cystic mass with density

similar to CSF and no enhancement with IV contrast. Expansion of nearby bone by remodelling is usually seen, confirming their chronic nature. Often associated with ventriculomegaly (in 64% of supratentorial and 80% of infratentorial cysts).

Convexity or middle fossa cysts exert mass effect on adjacent brain and may compress ipsilateral lateral ventricle and cause midline shift. Suprasellar, quadrigeminal plate, and midline posterior-fossa cysts may compress the third and fourth ventricle and cause hydrocephalus by obstructing the foramina of Monro or the Sylvian aqueduct.

MRI

Better than CT in differentiating the CSF contained in arachnoid cysts from the fluid of neoplastic cysts. May also show cyst walls.

Cisternograms and/or ventriculograms

Using either iodinated contrast or radionuclide tracers. Variable rate of opacification has resulted in difficulty correlating results with operative findings. Some cysts are actually diverticula, and may fill with radiotracer or contrast.

Treatment

Many (but not all) authors recommend not treating arachnoid cysts that do not cause mass effect or symptoms, regardless of their size and location. For incidentally discovered arachnoid cyst in an adult not considered for surgery: a single follow-up imaging study in 6-8 months is usually adequate to rule-out any changes (since they may grow in size). Subsequent studies may be done if concerning symptoms develop. Pediatric patients may need to be followed until adulthood.

Surgical treatment options are summarized in *Table 8-3*.

Table 8-3 Surgical treatment options for arachnoid cysts

Procedure	Advantages	Disadvantages
drainage by needle aspiration or burr hole evacuation	• simple • quick	• high rate of recurrence of cyst and neurologic deficit
craniotomy, excising cyst wall and fenestrating it into basal cisterns	• permits direct inspection of cyst (may help with diagnosis) • loculated cysts (rare) treated more effectively • avoids permanent shunt (in some cases)	• subsequent scarring may block fenestration allowing reaccumulation of cyst • flow through subarachnoid space may be deficient; many patients develop shunt dependency post-op • significant morbidity and mortality (may be due to abrupt decompression)

	• allows visualization of bridging vessels (small advantage)	
endoscopic cyst fenestration through a burr hole[8]	• as above	• as above
shunting of cyst into peritoneum or into vascular system	• definitive treatment • low morbidity/mortality • low rate of recurrence	• patient becomes "shunt dependent" • risk of infection of foreign body (shunt)

CYST SHUNTING

Probably the best overall treatment. For shunting into peritoneum, use a low pressure valve. If there is concurrent ventriculomegaly, one may simultaneously place a ventricular shunt (e.g. through a "Y" connector). Ultrasound, ventriculoscope, or image guidance may assist in locating suprasellar cysts. Shunting of middle fossa ACs may also be accomplished through the lateral ventricle, thus shunting both compartments[9].

✖ NB: in running the shunt tubing from the middle fossa, it should be routed behind the ear (do not tunnel caudally in front of ear to avoid injury to facial nerve).

SUPRASELLAR CYSTS

Treatments proposed include:

1. transcallosal cystectomy[10]
2. percutaneous ventriculo-cystostomy: procedure of choice of Pierre-Kahn et al.[4]. Performed via a paramedian coronal burr hole through the lateral ventricle and foramen of Monro (may be facilitated by using a ventriculoscope[8])
3. subfrontal approach (for fenestration or removal): dangerous and ineffective[4]

✖ ventricular drainage: ineffective (actually promotes cyst enlargement)

OUTCOME

Even following successful treatment a portion of the cyst may remain due to the remodeling of the bone and chronic shift of brain contents. Hydrocephalus may develop following treatment. Endocrinopathies tend to persist even after successful treatment of suprasellar cysts.

8.1.2. Arachnoid cysts, spinal

Almost always dorsal, most common in thoracic spine. With a ventral cyst, consider a neurenteric cyst (*see below*). Most are actually extradural and these are sometimes referred to as arachnoid diverticula - these may be associated with kyphoscoliosis in juveniles or with spinal dysraphism. Intradural arachnoid cysts may be congenital or may follow infection or trauma.

Usually asymptomatic, even if large.

TREATMENT

When indicated, treatment options include:

1. percutaneous procedures: may be done under MRI[11] or CT guidance. CT guidance usually requires use of intrathecal contrast to delineate the cyst
   A. needle aspiration
   B. needle fenestration[11]
2. open surgical resection or fenestration

8.2. Intracranial lipomas

Intracranial and intraspinal lipomas are felt to be of maldevelopmental origin[12 (p 706)] and may arise from failure of involution of the primitive meninges[13].

Epidemiology of intracranial lipomas

Incidence: 8 in 10,000 autopsies. Usually found in or near the midsagittal plane, particularly over the corpus callosum (lipomas in this region are frequently associated with agenesis of the corpus callosum, *see page 246*). The tuber cinereum and quadrigeminal plate are less frequently affected[14]. Rarely, the CP angle or cerebellar vermis may be involved. May occur in isolation, but also has been described in association with a number of congenital anomalies, including: trisomy 21, Pai's syndrome, frontal encephalocele, facial anomalies…. Other midline abnormalities may also be found: agenesis of the corpus callosum, myelomeningocele, and spina bifida[13].

Evaluation

May be diagnosed by CT, MRI (study of choice), and by ultrasound in

infants.

CT: Low density, may have peripheral calcification (difficult to appreciate on MRI)[13]. Differential diagnosis on CT: primarily between dermoid cyst, teratoma[15] and germinoma[13].

MRI: characteristic finding is a midline lesion with signal characteristics of fat (high intensity on T1WI, low intensity on T2WI).

Presentation

Often discovered incidentally. Large lipomas may be associated with seizures, hypothalamic dysfunction, or hydrocephalus (possibly from compression of the aqueduct). Associated findings that may or may not be directly related: mental retardation, behavioral disorders and headache.

Treatment

Direct surgical approach is seldom necessary for intracranial lipomas[15]. Shunting may be required for cases where hydrocephalus results from obstruction of CSF circulation[15].

8.3. Hypothalamic hamartomas

Key concepts:

> - rare, non-neoplastic congenital malformation, usually occurs in tuber cinereum
> - may be parahypothalamic (pedunculated) or intrahypothalamic (sessile)
> - presentation: precocious puberty, seizures (usually starting with gelastic seizures (brief unprovoked laughter)), developmental delay
> - treatment: GnRH analogs for precocious puberty. Latero-basal craniotomy for pedunculated lesions, transcallosal interforniceal approach for intrahypothalamic lesions, option of endoscopic approach for lesions ≤ 1.5 cm dia, stereotactic radiosurgery may be an alternative

Hypothalamic hamartomas[A] **(HH)** AKA diencephalic hamartomas or hamartomas of the tuber cinereum. Rare, non-neoplastic congenital malformations arising from inferior hypothalamus or tuber cinereum (floor of

the third ventricle between the infundibular stalk and the mammillary bodies). May occur as part of **Pallister-Hall syndrome** (genetics: AD inherited defect in GL[13] gene resulting in abnormally short GL[13] protein which participates in normal shaping of many organs).

A. hamartoma: an abnormal conglomeration of cells normally found in the same area

Clinical findings

1. specific types of seizures:
    A. **gelastic seizures** (brief episodes of unprovoked laughter[16]) are the most characteristic type and are the earliest seizure manifestation. Present in up to 92% of patients[17]. They are resistant to medical management and can lead to cognitive and behavioral deficits[18]. Not pathognomonic. A neocortical origin has been described[19]
    B. **epileptic encephalopathy**: gelastic fits gradually increase in frequency and other seizure types accrue: complex partial seizures, drop attacks, tonic seizures, tonic-clonic seizures, and secondarily generalized seizures. This phase is associated with marked deterioration of cognitive and behavioral abilities. Develops in 52% by a mean age of 7 years[17]
2. **precocious puberty**: believed to be due to release of gonadotropin-releasing hormone **(GnRH)** found within hamartoma cells[20]. HH are the most common CNS tumor to cause precocious puberty, other causes include: other CNS tumors (astrocytoma, ependymoma, pineal tumors (*see page 692*), optic/hypothalamic gliomas (especially in NFT patients)), CNS XRT, hydrocephalus, CNS inflammation, septo-optic dysplasia (*see page 247*), and chronic hypothyroidism
3. developmental delay: primarily in patients with seizure disorder (severity correlates with duration of seizures). 46% of patients have borderline intellectual function (mental retardation)
4. behavioral disturbances[21]: aggressive behavior, rage attacks…

Imaging

MRI: nonenhancing, isointense on T1WI, slightly hyperintense or isointense

on T2WI[22].

Pathology

Two subtypes of hypothalamic hamartomas[17, 22]:

1. **pedunculated** or parahypothalamic: narrower base attached to the floor of the hypothalamus (not arising within hypothalamus). No distortion of 3rd ventricle. Generally associated with precocious puberty more than seizures
2. **intrathalamic** or sessile: within hypothalamus (distorting the 3rd ventricle) or broad attachment to hypothalamus. More often associated with seizures. 66% have developmental delay, 50% have precocious puberty

Microscopic pathology: Clusters of disorganized small neurons surrounded by large pyramidal like neurons in an astrocyte-rich neuropil[23] (in contrast to the usual ganglion cells surrounded by oligodendrocytes found in the hypothalamus).

Treatment

Precocious puberty usually responds well to GnRH analogs[24].

Indications for surgery:

1. precocious puberty that fails to respond to medical therapy (GnRH analogs)
2. seizures that cannot be adequately controlled medically. Post-op seizure control is related to completeness of resection
3. neurologic deficit from mass effect of the tumor

Options:

1. surgical resection
   A. pedunculated lesions: approaches include[25] subtemporal, subfrontal, pterional, orbitozygomatic (most commonly recommended). Risks: cranial neuropathy, CVA[25]
   B. sessile lesions with intraventricular component: transcallosal anterior interforniceal approach[26-28]. Risks: memory impairment (forniceal injury), endocrine disturbances, weight gain[26, 28]
   C. neuroendoscopic approach: considered for HH $\leq$ 1.5 cm diameter[29]. Risks: 25% incidence of thalamic cerebrovascular injury

2. stereotactic radiosurgery: especially for small sessile lesions, subtotal resection, or patients refusing or not candidates for surgery. In small series, 3-year outcome showed improvement similar to surgical resection with less neurologic and endocrinologic morbidity[30, 31]

8.4. Neurenteric cysts

No uniformly accepted nomenclature. Working definition: CNS cyst lined by endot-helium primarily resembling that of the GI tract, or less often, respiratory tract. Congenital. Not true neoplasms. Most common alternate term: **enterogenous cyst**. Less common terms include: teratomatous cyst, intestinoma, archenteric cyst[32], enterogene cyst, and endodermal cyst. Usually affect the upper thoracic and lower cervical spine[33]. Associated developmental vertebral anomalies (e.g. diastematomyelia) are common[34]. Rarely intracranial (*see below*). Spinal neurenteric cysts **(NEC)** may have a fistulous or fibrous connection to the GI tract (through a spinal dysraphism) and some call these **endodermal sinus cysts**. Occurs as a result of persistence of the neurenteric canal (temporary duct between the notochord and the primitive gut (amniotic and yolk sacs) formed during week 3 of embryogenesis).

Intracranial neurenteric cysts: Rare, most common in p-fossa. Initially, may be difficult to rule-out metastasis from an extremely well-differentiated primary adenocarcinoma of unknown origin (absence of progressive disease suggests NEC). Locations:

1. posterior fossa
   A. cerebellopontine angle **(CPA)**[32]: usually intradural, extraaxial (case report of extradural lesion with bone destruction[35])
   B. in midline anterior to brainstem[33]
   C. cisterna magna[36]
2. supratentorial: only 15 case reports as of 2004[37]. Locations: suprasellar[38] (possible confusion with Rathke's cleft cyst), frontal lobe intraparenchymal[37], quadrigeminal plate region, dural-based extra-axial. Source of endoderm is controversial since the primitive foregut extends cranially only to the midbrain[39]. Theory: colloid cysts, Rathke cleft cysts, and supratentorial NECs may all arise from remnants of Seesel's pouch, a transient endodermally derived diverticulum of the cranial end of the

embryonic foregut[40]

Clinical

Most commonly present during the first decade of life[34]. Pain or myelopathy from the intraspinal mass are the most common presentations in older children and adults. Neonates and young children may present with cardiorespiratory compromise from an intrathoracic mass, or with cervical spinal cord compression[34]. Meningitis may occur from the fistulous tract, especially in newborns and infants.

Imaging

Intracranial NEC:

- CT: usually low density, nonenhancing[41]
- T1WI MRI: isointense or slightly hyperintense to CSF (may be hyperintense if there are blood products). T2WI isointense to CSF[41]. Nonenhancing

Histology

Most are simple cysts lined by cuboidal-columnar epithelium and mucin secreting goblet cells. Less common types of epithelium described include: stratified squamous and pseudostratified columnar, and ciliated epithelial cells. Mesodermal components may be present, including smooth muscle and adipose tissue, and some have called these teratomatous cysts[42, 43] which is not to be confused with teratomas which are true germinal cell neoplasms. May be histologically identical to colloid cysts.

Treatment

Spinal NEC: Surgical removal usually reverses the symptoms. Recurrence is uncommon with complete removal of cyst wall.

Intracranial NEC: Capsule adherent to brainstem may prevent complete resection, which predisposes to delayed recurrence. Apparently successful treatment by evacuation of contents and marsupialization has been reported (5 cases, mean follow-up: 5 yrs[44]). Incomplete removal requires long-term follow-up. Hydrocephalus is shunted if indicated.

8.5. Craniofacial development

8.5.1. Normal development

FONTANELLES

Anterior fontanelle: the largest fontanelle. Diamond shaped, 4 cm (AP) **x** 2.5 cm (transverse) at birth. Normally closes by age 2.5 yrs.

Posterior fontanelle: triangular. Normally closes by age 2-3 mos.

Sphenoid and mastoid fontanelles: small, irregular. Normally, former closes by age 2-3 mos, latter by age 1 yr.

CRANIAL VAULT

Growth: largely determined by growth of brain; 90% of adult head size is achieved by age 1 yr; 95% by age 6 yrs. Growth essentially ceases at age 7 yrs. By end of 2nd yr, bones have interlocked at sutures and further growth occurs by accretion and absorption.

Skull is unilaminar at birth. Diplöe appear by 4th yr and reach a maximum by age 35 yrs (when diploic veins form).

Mastoid process: formation commences by age 2 yrs, air cell formation occurs during 6th yr.

8.5.2. Craniosynostosis

Originally called craniostenosis. Incidence: ≈ 0.6/1000 live births.

Primarily a prenatal deformity, postnatal craniosynostosis **(CSO)** occurs uncommonly (postnatal causes consist primarily of positional alterations which may not represent true synostosis). CSO is rarely associated with hydrocephalus **(HCP)**[45]. The assertion that CSO may follow CSF shunting for HCP is unproven (*see page 328*). Other causes for failure of normal skull growth include lack of brain growth due to any of the causes of arrested development of the cerebral hemispheres (lissencephaly, micropolygyria, some cases of hydranencephaly…).

Treatment is usually surgical. In most instances, the indication for surgery is for cosmesis and to prevent the severe psychological effects of having a disfiguring deformity. However, with multiple CSO, brain growth may be

impeded by the unyielding skull. Also, ICP may be pathologically elevated, and although this is more common in multiple CSO[46], elevated ICP occurs in ≈ 11% of cases with a single stenotic suture. Coronal synostosis can cause amblyopia. Most cases of single suture involvement can be treated with linear excision of the suture. Involvement of multiple sutures or the skull base usually requires the combined efforts of a neurosurgeon and craniofacial surgeon, and may need to be staged in some cases. Risks of surgery include: blood loss, seizures, stroke.

DIAGNOSIS

Many cases of "synostosis" are really due to positional flattening (e.g. "lazy lamb-doid", *see below*). If this is suspected, instruct parents to keep head off of flattened area and recheck patient in 6-8 weeks: if it was positional, it should be improved, if it was CSO then it usually declares itself. The diagnosis of CSO may be aided by:

1. palpation of a bony prominence over the suspected synostotic suture (exception: lambdoidal synostosis, *see below*)
2. gentle firm pressure with the thumbs fails to cause relative movement of the bones on either side of the suture
3. plain skull x-rays:
   A. lack of normal lucency in center of suture. Some cases with normal x-ray appearance of the suture (even on CT) may be due to focal bony spicule formation[47]
   B. beaten copper calvaria (*see page 231*), sutural diastasis and erosion of the sella may be seen in cases of increased ICP[48]
4. CT scan:
   A. helps demonstrate cranial contour
   B. may show thickening and/or ridging at the site of synostosis
   C. will demonstrate hydrocephalus if present
   D. may show expansion of the frontal subarachnoid space[49]
   E. three-dimensional CT may help better visualize abnormalities
5. in questionable cases, a technetium bone scan can be performed[50]:
   - there is little isotope uptake by any of the cranial sutures in the first weeks of life
   - in prematurely closing sutures, increased activity compared to the other (normal) sutures will be demonstrated
   - in completely closed sutures, no uptake will be demonstrated
6. MRI: usually reserved for cases with associated intracranial abnormalities.

Often not as helpful as CT

7. measurements, such as occipito-frontal-circumference may not be abnormal even in the face of a deformed skull shape

Increased ICP

Evidence of increased ICP in the newborn with craniosynostosis include:

1. radiographic signs (on plain skull x-ray or CT, *see above*)
2. failure of calvarial growth (unlike the non-synostotic skull where increased ICP causes macrocrania in the newborn, here it is the synostosis that *causes* the increased ICP and lack of skull growth)
3. papilledema
4. developmental delay

TYPES OF CRANIOSYNOSTOSIS

SAGITTAL SYNOSTOSIS

The most common CSO affecting a single suture; 80% male. Results in **dolichocephaly** or **scaphocephaly** (boat shaped skull) with frontal bossing, prominent occiput, palpable keel-like sagittal ridge. OFC remains close to normal, but the biparietal diameter is markedly reduced.

Surgical treatment

Skin incision may be longitudinal or transverse. A linear "strip" craniectomy is performed, excising the sagittal suture from the coronal to the lambdoid suture, preferably within the first 3-6 months of life. The width of the strip should be at least 3 cm, no proof exists that interposing artificial substances (e.g. silastic sheeting over the exposed edges of the parietal bone) retards the recurrence of synostosis. Great care is taken to avoid dural laceration with potential injury to the underlying superior sagittal sinus. The child is followed and reoperated if fusion recurs before 6 months age. After ≈ 1 yr age, more extensive cranial remodelling is usually required.

CORONAL SYNOSTOSIS

Accounts for 18% of CSO, more common in females. In **Crouzon's syndrome** this is accompanied by abnormalities of sphenoid, orbital and facial bones (hypoplasia of mid-face), and in Apert's syndrome is accompanied by

syndactyly[51]. Unilateral coronal CSO → **plagiocephaly** with forehead on affected side flattened or concave above eye (normal side falsely appears to bulge abnormally), supra-orbital margin higher than normal side (on skull x-ray → **harlequin eye sign**). The orbit rotates out on the abnormal side, and can produce amblyopia. Without treatment, flattened cheeks develop and the nose deviates to the normal side (root of nose tends to rotate towards deformity).

Bilateral coronal CSO (usually in craniofacial dysmorphism with multiple suture CSO, e.g. Apert's) → **brachycephaly** with broad, flattened forehead (**acrocephaly**). When combined with premature closure of frontosphenoidal and frontoethmoidal sutures, results in foreshortened anterior fossa with maxillary hypoplasia, shallow orbits, progressive proptosis.

Surgical treatment

Simple strip craniectomy of the involved suture has been used, often with excellent cosmetic result. However, some argument that this may not be adequate has been presented. Therefore, a more current recommendation is to do frontal craniotomy (uni- or bilateral) with lateral canthal advancement by taking off orbital bar.

METOPIC SYNOSTOSIS

At birth, the frontal bone consists of two halves separated by the frontal or metopic suture. Abnormal closure results in a pointed forehead with a midline ridge (**trigonocephaly**). Many of these have a 19p chromosome abnormality and are retarded.

LAMBDOID SYNOSTOSIS

Epidemiology

Long considered a clinical rarity with a reported incidence range 1-9% of CSO[52], recent reports suggest a higher incidence of 10-20%[53] which may be due to an actual increased incidence, or simply to increased awareness or changing diagnostic criteria. More common in males (male:female = 4:1), and the right side is involved in 70% of cases. Usually presents between 3-18 months of age, but may be seen as early as 1-2 months of age.

Controversy exists regarding the actual criteria for this condition, and some authors differentiate between those cases which appear to have a primary abnormality of the lambdoid suture from those which may be due to positional

flattening, the so-called "**lazy lambdoid**". Others do not make this distinction, and sometimes refer to the condition as occipital plagiocephaly to avoid the need to implicate abnormalities of the lambdoid suture.

Positional flattening (or molding) may be produced by:

1. decreased mobility: patients who constantly lie supine with the head to the same side, e.g. cerebral palsy, mental retardation, prematurity, chronic illness
2. abnormal postures: congenital torticollis[54], congenital disorders of the cervical spine
3. intentional positioning: trend since 1992 to place newborns in a supine sleeping position to reduce the risk of sudden infant death syndrome **(SIDS)**[55], sometimes with a foam wedge to tilt the child to one side to reduce the risk of aspiration
4. intrauterine etiologies[56]: intrauterine crowding (e.g. from multiparous births or large fetal size), uterine anomalies

Clinical findings

Flattening of the occiput. May be unilateral or bilateral. If unilateral, it is sometimes termed **lambdoid plagiocephaly** which when severe also produces bulging of the ipsilateral forehead resulting in a "rhomboid" skull with the ipsilateral ear located anterior and inferior to the contralateral ear. The contralateral orbit and forehead may also be flattened. This may be confused with hemifacial microsomia or with plagiocephaly seen in unilateral coronal craniosynostosis. Bilateral lambdoid synostosis produces brachycephaly with both ears displaced anteriorly and inferiorly[52]. Unlike the palpable ridge of sagittal or coronal synostosis, an indentation may be palpated along the synostotic lambdoid suture (although a perisutural ridge may be found in some).

Diagnostic evaluation

The physical exam is the most important aspect of diagnosis. Skull x-ray may help differentiate (*see below*). If the skull x-ray is equivocal, prevent the infant from laying on the affected side for several weeks. A bone scan should be obtained if no improvement occurs (*see below*). In definite cases of synostosis, and for some cases of refractory positional flattening (which usually corrects with time, but may take up to 2 years) surgical treatment may be indicated.

Skull x-ray: Shows a sclerotic margin along one edge of the lambdoid suture in

70% of cases. Local “beaten copper cranium” **(BCC)** occasionally may be seen due to indentations in the bone from underlying gyri which may be due to locally increased ICP. BCC produces a characteristic mottled appearance of the bone with lucencies of varying depth having round and poorly marginated edges. BCC correlates with generalized ↑ ICP only when it is seen with sellar erosion and sutural diastasis[48].

CT scan: Bone windows may show eroded or thinned inner table in the occipital region in 15-20% of cases[53], > 95% are on the side of the involvement. The suture may appear closed. Brain windows show parenchymal brain abnormalities in < 2%: heterotopias, hydrocephalus, agenesis of the corpus callosum; but ≈ 70% will have significant expansion of the frontal subarachnoid space (may be seen in synostosis of other sutures, *see above*).

Bone scan: Isotope uptake in the lambdoid suture increases during the first year, with a peak at 3 months of age[57] (following the usual inactivity of the first weeks of life). The findings with synostosis are those typical for CSO (*see page 229*).

Treatment

Early surgical treatment is indicated in cases with severe craniofacial disfigurement or those with evidence of increased ICP. Otherwise, children may be managed non-surgically for 3-6 months. The majority of cases will remain static or will improve with time and simple nonsurgical intervention. Approximately 15% will continue to develop a significant cosmetic deformity.

Nonsurgical management[58]:

Although improvement can usually be attained, some degree of permanent disfigurement is frequent.

Repositioning will be effective in ≈ 85% of cases. Patients are placed on the unaffected side or on the abdomen. Infants with occipital flattening from torticollis should have aggressive physical therapy and resolution should be observed within 3-6 months.

More severe involvement may be treated with a trial of molding helmets[59] (however, no controlled study has proven the efficacy).

Surgical treatment:

Required in only ≈ 20% of cases. The ideal age for surgery is between 6 and 18 months. The patient is positioned prone on a well-padded cerebellar headrest (the face should be lifted and gently massaged every ≈ 30 minutes by the

anesthesiologist to prevent pressure injuries).

Surgical options range from simple unilateral craniectomy of the suture to elaborate reconstruction by a craniofacial team.

Linear craniectomy extends from the sagittal suture to the asterion is often adequate for patients ≤ 12 weeks of age without severe disfigurement. Great care is taken to avoid dural laceration near the asterion which is in the region of the transverse sinus. The excised suture demonstrates an internal ridge. Better results are obtained with earlier surgery, more radical surgery may be necessary after the age of 6 months.

Average blood loss for uncomplicated cases is 100-200 ml and therefore transfusion is often required.

MULTIPLE SYNOSTOSES

Fusion of many or all cranial sutures → **oxycephaly** (tower skull with undeveloped sinuses and shallow orbits). These patients have elevated ICP.

CRANIOFACIAL DYSMORPHIC SYNDROMES

Over 50 syndromes have been described, *Table 8-4*, shows a few selected ones.

A number of craniosynostosis syndromes are due to mutations in the FGFR (fibro-blast growth factor receptor) genes. FGFR generelated craniosynostosis syndromes include some classic syndromes (Apert, Crouzon, Pfeiffer…) as well as several newer entities (Beare-Stevenson, Muenke, Jackson-Weiss syndromes). All exhibit autosomal dominant inheritance.

Table 8-4 Selected craniofacial dysmorphic syndromes (modified[60 (p 123-4)])

Syndrome	--- Genetics ---		Craniofacial findings	Associated findings
	Sporadic	Inherited		
Crouzon (cranio-facial dysostosis)	yes (25%)	FGFR AD*	CSO of coronal & basal skull sutures, maxillary hypoplasia, shallow orbits, proptosis	HCP rare
Apert (acrocephalosyndactyly)	yes (95%)	FGFR AD	same as Crouzon	syndactyly of digits 2,3,4; shortened UE, HCP common
Kleeblattschadel	yes	AD	CSO with trilobular skull	isolated, or with Apert's or thanatophoric dwarfism

* abbreviations: AD = autosomal dominant; FGFR = fibroblast growth factor receptor gene-related; CSO = craniosynostosis; HCP = hydrocephalus; UE = upper extremities

8.5.3. Encephalocele

Cranium bifidum is a defect in the fusion of the cranial bone, it occurs in the mid-line, and is most common in the occipital region. If meninges and CSF herniate through the defect, it is called a meningocele. If meninges and cerebral tissue protrude, it is called an encephalocele.

Encephalocele AKA **cephalocele** is an extension of intracranial structures outside of the normal confines of the skull. One case was seen for every five cases of spinal myelomeningoceles[61]. A nasal polypoid mass in a newborn should be considered an encephalocele until proven otherwise. See also *Differential diagnosis,* page 1229.

CLASSIFICATION

System based on Suwanwela and Suwanwela[62]:

1. occipital: often involves vascular structures
2. cranial vault: comprises ≈ 80% of encephaloceles in Western hemisphere
   A. interfrontal
   B. anterior fontanelle
   C. interparietal: often involves vascular structures
   D. temporal
   E. posterior fontanelle
3. fronto-ethmoidal: AKA sincipital; 15% of encephaloceles; external opening into face in one of the following 3 regions:
   A. nasofrontal: external defect in the nasion
   B. naso-ethmoidal: defect between nasal bone and nasal cartilage
   C. naso-orbital: defect in the anteroinferior portion of medial orbital wall
4. basal: 1.5% of encephaloceles; (*see below*)
   A. transethmoidal: protrudes into nasal cavity through defect in cribriform plate
   B. spheno-ethmoidal: protrudes into posterior nasal cavity
   C. transsphenoidal: protrudes into sphenoid sinus or nasopharynx through patent craniopharyngeal canal (foramen cecum)
   D. fronto-sphenoidal or spheno-orbital: protrudes into orbit through superior orbital fissure
5. posterior fossa: usually contains cerebellar tissue and ventricular component

BASAL ENCEPHALOCELE

The only group that does not produce a visible soft tissue mass. May present

as CSF leak or recurrent meningitis. May be associated with other craniofacial deformities, including: cleft lip, bifid nose, opticnerve dysplasia, coloboma and microphthalmia, hypothalamic-pituitary dysfunction.

Iniencephaly is characterized by defects around the foramen magnum, rachischisis and retrocollis. Most are stillborn, some survive up to age 17.

ETIOLOGY

Two main theories:

1. arrested closure of normal confining tissue allows herniation through persistent defect
2. early outgrowth of neural tissue prevents normal closure of cranial coverings

TREATMENT

Occipital encephalocele

Surgical excision of the sac and its contents with water-tight dural closure. It must be kept in mind that vascular structures are often included in the sac. Hydrocephalus is often present and may need to be treated separately.

Basal encephalocele

Caution: a transnasal approach to a basal encephalocele (even for biopsy alone) may be fraught with intracranial hemorrhage, meningitis, or persistent CSF leak. Usually a combined intracranial approach (with amputation of the extracranial mass) and trans-nasal approach is used.

OUTCOME

Occipital encephalocele

The prognosis is better in occipital meningocele than in encephalocele. The prognosis is worse if a significant amount cerebral tissue is present in the sac, if the ventricles extend into the sac, or if there is hydrocephalus. Less than ≈ 5% of infants with encephalocele develop normally.

8.6. Chiari malformation

The term "Chiari malformation" (after pathologist, Hans Chiari) is preferred for type 1 malformations, with the commonly used term "Arnold-Chiari malformation" reserved for type 2 malformation.

The Chiari malformations consists of four types of hindbrain abnormalities, probably unrelated to each other. The majority are types 1 or 2 (*see Table 8-5*), a very limited number of cases comprise the remaining types.

Table 8-5 Comparisons of Chiari type 1 and 2 anomalies (adapted[63])

Finding	Chiari type 1 (*see below*)	Chiari type 2 (*see page 238*)
caudal dislocation of medulla	unusual	yes
caudal dislocation into cervical canal	tonsils	inferior vermis, medulla, 4th ventricle
spina bifida (myelomeningocele)	may be present	rarely absent
hydrocephalus	may be absent	rarely absent
medullary "kink"	absent	present in 55%
course of upper cervical nerves	usually normal	usually cephalad
usual age of presentation	young adult	infancy
usual presentation	cervical pain, suboccipital H/A	progressive hydrocephalus, respiratory distress

TYPE 1 CHIARI MALFORMATION

Key concepts:

- a heterogeneous entity with the common feature of impaired CSF circulation through the foramen magnum
- cerebellar tonsillar herniation on MRI: criteria vary, > 5 mm below the foramen magnum is often cited, but is neither essential nor diagnostic of the condition
- treatment, when indicated, is surgical, but aspects of what that surgery should entail are controversial (enlargement of foramen magnum is usually involved)
- associated with syringomyelia in 30-70% which almost always improves with treatment of the Chiari malformation

AKA primary cerebellar ectopia[64], AKA adult Chiari malformation (since it tends to be diagnosed in the 2nd or 3rd decade of life). A heterogeneous group of conditions, with the underlying commonality of disruption of normal CSF flow through the foramen magnum **(FM)**. Some cases are congenital, but others are acquired.

Classically described as a rare abnormality restricted to caudal displacement of cerebellum with tonsillar herniation below the foramen magnum (see *MRI* below for criteria) and "peg-like elongation of tonsils". Unlike Chiari type 2, the medulla is not caudally displaced (some authors disagree on this point[65]), the brainstem is not involved, lower cranial nerves are not elongated, and upper cervical nerves do not course cephalad. Syringomyelia[A] of the spinal cord is present in 30-70%[66]. Hydrocephalus occurs in 7-9% of patients with Chiari type 1 malformation and syringomyelia[66].

A. true hydromyelia probably doesn't occur. CSF flow has not been documented in man, and it is generally not possible to find communication between the syrinx and the central canal in Chiari 1 patients

Cerebellar tonsil descent below FM with impaction, while common, is no longer a sine qua non of diagnosis.

Etiology: may be associated with

1. a small posterior fossa
   A. underdevelopment of the occipital bone
   B. low lying tentorium (the roof of the p-fossa)
   C. thickened or elevated occipital bone (the floor of the p-fossa)
   D. space occupying lesion in p-fossa: arachnoid cyst (retrocerebellar or supracerebellar[67]), tumor (e.g. FM meningioma or cerebellar astrocytoma), hypervascular dura
2. has been described with just about anything that takes up intracranial space
   A. chronic subdural hematomas
   B. hydrocephalus
3. following lumboperitoneal shunt (*see page 317*) or multiple (traumatic) LPs[68]: acquired Chiari 1 malformation (usually asymptomatic)
4. arachnoid web or scar or fibrosis around brainstem and tonsils near FM

5. abnormalities of the upper cervical spine
    A. hypermobility of the craniovertebral junction
    B. Klippel-Feil syndrome
    C. occipitalization of the atlas
    D. anterior indentation at foramen magnum: e.g. basilar invagination or retroversion of the odontoid process
6. Ehlers-Danlos syndrome
7. craniosynostosis: especially cases involving all sutures
8. retained rhomboid roof: rare

Epidemiology

Average age at presentation is 41 years (range: 12-73 yrs). Slight female preponderance (female:male = 1.3:1). Average duration of symptoms clearly related to Chiari malformation is 3.1 yrs (range: 1 month-20 yrs); if nonspecific complaints, e.g. H/A, are included, this becomes 7.3 years[69]. This latency is probably lower in the MRI era.

Clinical

Patients with Chiari type 1 malformation may present due to any or all of the following:

1. compression of brain stem at the level of the foramen magnum
2. hydrocephalus
3. syringomyelia
4. isolation of the intracranial pressure compartment from the spinal compartment causing transient elevations of intracranial pressure
5. 15-30% of patients with adult Chiari malformation are asymptomatic[70]

Symptoms

The most common symptom is pain (69%), especially headache which is usually felt in the suboccipital region (*see Table 8-6*). H/A are often brought on by neck extension or valsalva maneuver. Weakness is also prominent, especially unilateral grasp. Lhermitte's sign may also occur. Lower extremity involvement usually consists of bilateral spasticity.

Table 8-6 Presenting symptoms in Chiari 1 malformation (71 cases[65])

Symptom	%

pain	69%
H/A	34%
neck (suboccipital, cervical)	13%
girdle	11%
arm	8%
leg	3%
weakness (1 or more limbs)	56%
numbness (1 or more limbs)	52%
loss of temperature sensation	40%
painless burns	15%
unsteadiness	40%
diplopia	13%
dysphasia	8%
tinnitus	7%
vomiting	5%
dysarthria	4%
miscellaneous	
dizziness	3%
deafness	3%
fainting	3%
facial numbness	3%
hiccough	1%
facial hyperhidrosis	1%

Table 8-7 Presenting signs in Chiari I malformation (127 patients[69])

Sign	%
hyperactive lower extremity reflexes	52%
nystagmus*	47%
gait disturbance	43%
hand atrophy	35%
upper extremity weakness	33%
“cape” sensory loss	31%
cerebellar signs	27%

hyperactive upper extremity reflexes	26%
lower cranial nerve dysfunction	26%
Babinski sign	24%
lower extremity weakness	17%
dysesthesia	17%
fasciculation	11%
Horner's sign	6%

* classically: downbeat nystagmus on vertical movement, and rotatory nystagmus on horizontal movement; also includes oscillopsia[72]

Signs

See *Table 8-7*. Three main patterns of clustering of signs[65]:

1. foramen magnum compression syndrome (22%): ataxia, corticospinal and sensory deficits, cerebellar signs, lower cranial nerve palsies. 37% have severe H/A
2. central cord syndrome (65%): dissociated sensory loss (loss of pain & temperature sensation with preserved touch & JPS), occasional segmental weakness, and long tract signs (syringomyelic syndrome[71]). 11% have lower cranial nerve palsies
3. cerebellar syndrome (11%): truncal and limb ataxia, nystagmus, dysarthria

Downbeat nystagmus is considered a characteristic of this condition. 10% will have a normal neurologic exam with occipital H/A as their only complaint. Some patients may present primarily with spasticity.

Natural history

The natural history is not known with certainty (only 2 reports on "natural history"). A patient may remain stable for years, with intermittent periods of deterioration. Rarely, spontaneous improvement may occur (debated).

Evaluation

Plain x-rays

Of 70 skull x-rays, only 36% were abnormal (26% showed basilar impression, 7% platybasia, and 1 patient each with Paget's and concave clivus); in 60 C-spine x-rays, 35% were abnormal (including assimilation of atlas,

widened canal, cervical fusions, agenesis of posterior arch of atlas).

MRI

Diagnostic test of choice. Easily shows many of the classic abnormalities described earlier, including tonsillar herniation, as well as hydrosyringomyelia which occurs in 20-30% of cases. Also demonstrates ventral brain stem compression when present. Other findings include: hydrocephalus, empty sella.

Tonsillar herniation: Criteria for the descent of the tonsillar tips below the foramen magnum **(FM)** to diagnose Chiari type 1 malformation have gone through a number of reconsiderations.

Σ Tonsillar herniation identified radiographically is of limited prognostic value in diagnosing Chiari I malformation, and requires clinical correlation.

Initially, > **5 mm** was defined as clearly pathologic[73] (with 3-5 mm being borderline). Barkovich[74] found tonsillar positions as shown in *Table 8-8*, and *Table 8-9* shows the effect of utilizing 2 vs. 3 mm as the lowest normal position.

Table 8-8 Location of cerebellar tonsils below foramen magnum[74]

Group	Mean*	Range
normal	1 mm above	8 mm above to 5 mm below
Chiari I	13 mm below	3-29 mm below

* based on measurements in 200 normals and 25 Chiari I patients taken in relation to the lower part of the foramen magnum

Table 8-9 Criteria for Chiari I[74]

Criteria for lowest extent of tonsils accepted as normal	Sensitivity for Chiari I	Specificity for Chiari I
2 mm below FM	100%	98.5%
3 mm below FM	96%	99.5%

The tonsils normally ascend with age[75] as shown in *Table 8-10*.

Patients with syringohydromyelia without hindbrain herniation that responded to p-fossa decompression have been described[76] (so-called "**Chiari zero malformation**"). Conversely, 14% of patients with tonsillar herniation > 5 mm are asymptomatic[77] (average extent of ectopia in this group was 11.4 ± 4.86 mm).

Potentially more significant than the absolute tonsillar descent is the amount of compression of the brainstem at the FM, best appreciated on axial T2WI MRI though the FM. Complete obliteration of CSF signal and compression of the brainstem at the FM by impacted tonsils is a common significant finding.

Cine MRI: AKA CSF flow study. May demonstrate blockage of CSF flow at FM. Not widely available. Accuracy is not high, therefore usually does not alter management.

Table 8-10 Tonsillar position relative to FM at various ages[75]

Age (years)	Normal (mm)*	2 S.D.† (mm)
0-9	–1.5	–6
10-19	–0.4	–5
20-29	–1.1	
30-39	0.0	–4
40-49	0.1	
50-59	0.2	
60-69	0.2	
70-79	0.6	
80-89	1.3	–3

* negative number indicates distance below FM

† S.D. = standard deviation. Descent > 2 S.D. beyond normal is suggested as a criteria for tonsillar ectopia

Myelography

Only 6% false negative. Must run dye all the way up to the foramen magnum.

CT

CT has difficulty evaluating the foramen magnum region due to bony artifact. When combined with intrathecal iodinated contrast (myelogram), reliability improves. Findings: tonsillar descent and/or ventricular dilatation.

TREATMENT

Indications for surgery

Since patients respond best when operated on within 2 years of the onset of symptoms (see *Operative results* below), early surgery is recommended for symptomatic patients. Asymptomatic patients may be followed and operated upon if and when they become symptomatic. Patients who have been symptomatic and stable for years may be considered for observation, with surgery indicated for signs of deterioration.

Surgical techniques

The most frequently performed operation is posterior fossa decompression (suboccipital craniectomy), with or without other procedures (usually combined with dural patch grafting and cervical laminectomy of C1, sometimes to C2 or C3). Options for grafts: same incision (pericranium), separate incision (e.g. or fascia lata), and allograft (avoided by many authors because of dissatisfaction with ability to provide water-tight closure and because of infectious risks.

Goals of surgery: decompress the brain stem and reestablish normal flow of CSF at the craniocervical junction.

The patient is positioned prone on chest rolls with the head in a Mayfield head-holder or in a horseshoe headrest. Flex the neck to open the interspace between the occiput and posterior arch of C1. The shoulders are retracted inferiorly with adhesive tape. If a fascia lata graft is to be taken, elevate one thigh on a sandbag. A midline incision from inion to ≈ C2 spinous process is made. The removal of bone above the foramen magnum should be ≈ 3 cm high by ≈ 3 cm wide (keep the posterior-fossa part of these operations small, the main thrust is to open the foramen magnum to decompress the tonsils and an upper cervical laminectomy; the compression is <u>not</u> in the p-fossa). Excessive removal of occipital bone may allow the cerebellar hemispheres to herniate through the opening, and create additional problems. If a pericranial graft is to be taken, it should be harvested at this time to reduce the amount of blood entering the subsequent dural opening[78].

Pericranial graft can be procured without extending the incision about the inion using the technique of Dr. Robert Ojemann[78] with subgaleal dissection and using a monopolar cautery with a bent tip to incise the periosteum and then a Penfield #1 dissector to free it from the bone surface.

Open the dura in a "Y" shaped incision, and excise the triangular top flap. CAUTION: the transverse sinuses are usually abnormally <u>low</u> in Chiari malformations. Suture the patch graft to provide more room for the contents

(tonsils + medulla).

An option that is sometimes used in pediatrics is to not initially open the dura but to lyse constricting bands over the dura at the foramen magnum and then and use intraoperative ultrasound to determine if there is adequate room for CSF flow, the dura is then opened only if there is not.

Historical procedures that have been appended to the above: plugging the obex (with muscle or teflon), drainage of syrinx if present (fenestration, usually through dorsal root entry zone, with or without stent or shunt), 4th ventricular shunting, terminal ventriculostomy, and opening foramen of Magendie if obstructed (see reference for illustrations[71]). Current recommendations are that these or other additional procedures beyond dural patch grafting are usually not warranted.

Some authors repeatedly admonish not to attempt to remove adhesions binding the tonsils together (to avoid injuring vital structures, including PICAs). Others recommend cautiously separating the tonsils and even shrinking them down with bipolar cautery.

In cases with ventral brain-stem compression, some authors advocate performing a transoral clivus-odontoid resection as they feel these patients may potentially deteriorate with posterior fossa decompression alone[79]. Since this deterioration was reversible with odontoidectomy, it may be reasonable to perform this procedure on patients who show signs of deterioration or progression of basilar impression on serial MRIs after posterior fossa decompression.

Operative findings

See Table 8-11. Tonsillar herniation is present in all cases (by definition); the most common position being at C1 (62%). Fibrous adhesions between dura, arachnoid and tonsils with occlusion of foramina of Luschka and Magendie in 41%. The tonsils separated easily in 40%.

Table 8-11 Operative findings in Chiari I (71 patients[65])

Finding	%
tonsillar descent	100%
below foramen magnum	4%
C1	62%
C2	25%

C3	3%
unspecified level	6%
adhesions	41%
syringomyelia	32%
dural band (at foramen magnum or C1 arch)	30%
vascular abnormalities*	20%
skeletal abnormalities	
inverted foramen magnum	10%
keel of bone	3%
C1 arch atresia	3%
occipitalization of C1 arch	1%
cervicomedullary “hump”	12%

* vascular abnormalities: PICA dilated or abnormal course in 8 patients (PICA often descends to lower margin of tonsils[71]); large dural venous lakes in 3

SURGICAL COMPLICATIONS

After suboccipital craniectomy plus C1-3 laminectomy in 71 patients, with dural patch grafting in 69, one death due to sleep apnea occurred 36 hrs post-op. Respiratory depression was the most common post-op complication (in 10 patients), usually within 5 days, mostly at night. Close respiratory monitoring is therefore recommended[65]. Other risks of the procedure include: CSF leak, herniation of cerebellar hemispheres, vascular injuries (to PICA…).

OPERATIVE RESULTS

See *Table 8-12*. Patients with pre-op complaints of pain generally respond well to surgery. Weakness is less responsive to surgery, especially when muscle atrophy is present[79]. Sensation may improve when the posterior columns are unaffected and the deficit is due to spinothalamic involvement alone.

Rhoton feels that the main benefit of operation is to arrest progression.

The most favorable results occurred in patients with cerebellar syndrome (87% showing improvement, no late deterioration). Factors that correlate with a worse outcome are the presence of atrophy, ataxia, scoliosis, and symptoms lasting longer than 2 years[79].

Table 8-12 Long-term follow-up after surgery for Chiari I malformation (69 patients, 4 years mean F/U[65])

early improvement of pre-op symptoms	82%
percent of above that relapsed*	21%
early improvement of pre-op signs	70%
no change from pre-op status	16%
worse than pre-op	0

* these patients deteriorated to pre-op status (none deteriorated further) within 2-3 years of surgery; relapse occurred in 30% with foramen magnum compression syndrome, and in 21% with central cord syndrome

TYPE 2 (ARNOLD)-CHIARI MALFORMATION

Key concepts:

- usually associated with myelomeningocele, often accompanied by hydrocephalus
- pathology includes: caudally displaced cervicomedullary junction, small posterior fossa, tectal beaking. Is probably not due to tethering
- major clinical findings: swallowing difficulties, apnea, stridor, opisthotonos, downbeat nystagmus
- when symptomatic: always check the shunt first! Then, consider surgical decompression (which cannot correct intrinsic brainstem abnormalities)

Usually associated with myelomeningocele **(MM)**, or rarely spina bifida occulta.

PATHOPHYSIOLOGY

Probably does not result from tethering of the cord by the associated MM. More likely due to primary dysgenesis of the brainstem with multiple other developmental anomalies[80].

Major findings

Caudally dislocated cervicomedullary junction, pons, 4th ventricle and medulla. Cerebellar tonsils located at or below the foramen magnum. Replacement of normal cervicomedullary junction flexure with a “kink-like deformity”.

Other possible associated findings:

1. beaking of tectum
2. absence of the septum pellucidum with enlarged interthalamic adhesion:

absence of the septum pellucidum is thought to be due to necrosis with resorption secondary to hydrocephalus, and not a congenital absence[81] (p 178)

3. poorly myelinated cerebellar folia
4. hydrocephalus: present in most
5. heterotopias
6. hypoplasia of falx
7. microgyria
8. degeneration of lower cranial nerve nuclei
9. bony abnormalities:
   A. of cervicomedullary junction
   B. assimilation of atlas
   C. platybasia
   D. basilar impression
   E. Klippel-Feil deformity: *see page 253*
10. hydromyelia
11. craniolacunia of the skull (*see below*)

PRESENTATION

Findings are due to brain stem and lower cranial nerve dysfunction. Onset is rare in adulthood. The presentation of neonates differs substantially from older children, and neonates were more likely to develop rapid neurological deterioration with profound brain stem dysfunction over a period of several days than were older children in whom symptoms were more insidious and rarely as severe[82].

Findings include[82, 83]:

1. swallowing difficulties (neurogenic dysphagia) (69%)[84]. Manifests as poor feeding, cyanosis during feeding, nasal regurgitation, prolonged feeding time, or pooling of oral secretions. Gag reflex often decreased. More severe in neonates
2. apneic spells (58%): due to impaired ventilatory drive. More common in neonates
3. stridor (56%): more common in neonates, usually worse on inspiration (abductor and occasionally adductor vocal cord paralysis seen on laryngoscopy) due to 10th nerve paresis; usually transient, but may progress to respiratory arrest

4. aspiration (40%)
5. arm weakness (27%) that may progress to quadriparesis[85]
6. opisthotonos (18%)
7. nystagmus: especially downbeat nystagmus
8. weak or absent cry
9. facial weakness

DIAGNOSTIC EVALUATION

Skull films

May demonstrate cephalofacial disproportion from congenital HCP. **Craniolacunia** (AKA **lückenschädel**) in 85% (round defects in the skull with sharp borders, separated by irregularly branching bands of bone; <u>not</u> due to increased ICP). Low lying internal occipital protuberance (foreshortened posterior fossa). Enlarged foramen magnum in 70%; elongation of upper cervical lamina[63].

CT and/or MRI findings

- primary findings
  - A. "Z" bend deformity of medulla*
  - B. cerebellar peg
  - C. tectal fusion ("tectal beaking")
  - D. enlarged massa intermedia (interthalamic adhesion)*
  - E. elongation/cervicalization of medulla
  - F. low attachment of tentorium
- associated findings
  - A. hydrocephalus
  - B. syringomyelia in the area of the cervicomedullary junction (reported incidence in pre MRI era[79] ranges from 48-88%)
  - C. trapped fourth ventricle
  - D. cerebellomedullary compression
  - E. agenesis/dysgenesis of corpus callosum*

* items with an asterisk are best appreciated on MRI

Laryngoscopy

Performed in patients with stridor to rule out croup or other upper respiratory tract infection.

TREATMENT

- insert CSF shunt for hydrocephalus (or check function of existing shunt)
- if neurogenic dysphagia, stridor, or apneic spells occur, expeditious posterior fossa decompression is recommended (*see below*) (required in 18.7% of MM patients[83]); before recommending decompression, always make sure the patient has a functioning shunt!

Surgical decompression

NB: it has been argued that part of the explanation for the poor operative results in infants is that many of the neurological findings may be due in part to intrinsic (uncorrectable) abnormalities which surgical decompression cannot improve[86, 87]. A dissenting view is that the histologic lesions are due to chronic brain stem compression and concomitant ischemia, and that expeditious brain stem decompression should be carried out when any of the following critical warning signs develop: neurogenic dysphagia, stridor, apneic spells[82].

Surgical technique:

Decompression of cerebellar tonsils, usually with dural graft to decompress dura. Patients is placed prone, with the neck flexed. A suboccipital craniectomy is combined with a cervical laminectomy which must be carried down to the bottom of the tonsillar tip[85]. A thick constricting dural band is usually found between the C1 arch and foramen magnum. The dura is opened in a “Y” shaped incision. Caution when opening the dura above the level of the foramen magnum in infants as they have a well developed occipital sinus and may have large dural lakes[83]. DO NOT attempt to dissect tonsils from underlying medulla. In cases with a significant syringomyelic cavity, a syringo-subarachnoid shunt is placed[82].

Tracheostomy (usually temporary) is recommended if stridor and abductor laryngeal palsy were present pre-op. Close post-op respiratory monitoring is needed for obstruction and reduced ventilatory drive (mechanical ventilation is indicated for hypoxia or hypercarbia).

OUTCOME

68% had complete or near complete resolution of symptoms, 12% had mild

to moderate residual deficits, and 20% had no improvement (in general, neonates fared worse than older children)[82].

Respiratory arrest is the most common cause of mortality (8 of 17 patients who died), with the rest due to meningitis/ventriculitis (6 patients), aspiration (2 patients), and biliary atresia (1 patient)[83].

In follow-up ranging 7 mos-6 yrs, 37.8% mortality in operated patients.

Pre-op status and the rapidity of neurologic deterioration were the most important prognosticators. Mortality rate is 71% in infants having cardiopulmonary arrest, vocal cord paralysis or arm weakness within 2 weeks of presentation; compared to 23% mortality in patients with a more gradual deterioration. Bilateral vocal cord paralysis was a particularly poor prognosticator for response to surgery[82].

OTHER CHIARI MALFORMATIONS

CHIARI TYPE 3

Rare. The most severe form. Displacement of posterior fossa structures, with cerebellum herniated through foramen magnum into cervical canal, often with a high cervical or suboccipital encephalomeningocele. Usually incompatible with life.

CHIARI TYPE 4

Cerebellar hypoplasia without cerebellar herniation.

8.7. Dandy Walker malformation

Definition: an enlarged posterior fossa with complete or partial agenesis of the cerebellar vermis and cystic dilatation of the fourth ventricle which is distorted and encased in a membrane. The anomaly was first described by Dandy & Blackfan in 1914, and was named Dandy Walker malformation forty years later by Benda to acknowledge Taggart and Walker's contributions in 1942[88].

Differential diagnosis

Disorders with posterior fossa CSF collections include[148]:

1. Dandy Walker malformation **(DWM)**

2. Dandy Walker variant **(DWV)**: vermian hypoplasia and cystic dilatation of the fourth ventricle, without enlargement of the posterior fossa
3. persistent Blake's pouch cyst **(BPC)**: tetraventricular hydrocephalus, communicating 4th ventricle and posterior fossa cyst, with or without hypoplasia of both the cerebellar vermis and the medial aspects of the cerebellar hemispheres
4. retrocerebellar arachnoid cyst: anteriorly displaces the 4th ventricle and cerebellum, which can produce significant mass effect
5. Joubert's syndrome: absence or underdevelopment of the cerebellar vermis
6. mega cisterna magna: enlarged posterior fossa secondary to an enlarged cisterna magna with a normal vermis and fourth ventricle)

Differentiating features: DWM and DWV are difficult to distinguish, and may represent a continuum of developmental anomalies that are grouped together as **Dandy Walker complex**[89].

Retrocerebellar arachnoid cysts and BPCs may mimic DWM, but these do not have vermian agenesis and the cyst does not open into the 4th ventricle. The position of the choroid plexus of the fourth ventricle is normal in arachnoid cysts, absent in Dandy Walker malformations, and displaced into the superior cyst wall in BPC. An intrathecal enhanced CT scan (performed after instilling iodinated contrast into a ventricular catheter) would identify a mega cisterna magna which communicates with the ventricles, while DWM and most but not all arachnoid cysts do not.

Pathophysiology

The etiology of DWM is unknown. Multiple unsatisfactory theories have been abandoned. DWM is likely due to dysembryogenesis, secondary to insults of varying severity to the cerebellum and 4th ventricle. This results in agenesis of the cerebellar vermis with a large posterior fossa cyst communicating with an enlarged 4th ventricle[88, 89].

Hydrocephalus occurs in 70-90% of cases, and Dandy Walker malformation is present in 2-4% of all cases of hydrocephalus.

Risk factors and epidemiology

Gestational exposure to rubella, CMV, toxoplasmosis, warfarin, alcohol, and isotretinoin are thought to be predisposing factors. Autosomal recessive inheritance has been identified in a few cases, but a genetic basis is lacking in

most. Incidence: 1 per 25,000-35,000 live births[88]. Male:female=1:3.

Associated abnormalities

CNS abnormalities include agenesis of the corpus callosum in 17%[90], and occipital encephalocele in 7%. Other findings include heterotopias, spina bifida, syringomyelia, microcephaly, dermoid cysts, porencephaly, and Klippel-Feil deformity. Most have an enlarged posterior fossa with elevation of the torcular herophili. Atresia of the foramina of Magendie and Luschka may occur[91].

Systemic abnormalities include[90]: facial abnormalities (e.g. angiomas, cleft palates, macroglossia, facial dysmorphia), ocular abnormalities (e.g. coloboma, retinal dysgenesis, microphthalmia), and cardiovascular anomalies (e.g. septal defects, patent ductus arteriosus, aortic coarctation, dextrocardia). Note: be aware of the possibility of a cardiac abnormality when considering surgery on these patients.

Treatment

Early decompression of ventriculomegaly is recommended to achieve maximum cognitive development. In the absence of hydrocephalus, DWM may be followed. When treatment is necessary, the posterior fossa cyst must be shunted. Shunting the lateral ventricles alone is contraindicated because of the risk of upward herniation[92]. However, it is important to confirm patency of the cerebral aqueduct, otherwise the supratentorial ventricles need to be shunted concomitantly. Varying reports exist regarding rates of associated aqueductal stenosis, although it is widely believed to be rare.

Another option once used commonly is excision of the obstructing membrane. This has fallen out of favor due to its associated risks of morbidity and mortality. However, it remains an option for patients with frequent shunt malfunctions.

Newer treatments include endoscopic third ventriculostomy in cases where the aqueduct is patent, however further study is necessary[93, 94].

Prognosis

Prognosis ranges widely as there are various levels of severity of the malformation. Some pediatric neurosurgical literature quotes 12-50% mortality rates, although this is improving with modern shunting techniques. Only 50% have normal IQ. Ataxia, spasticity, and poor fine motor control are common.

Seizures occur in 15%.

8.8. Aqueductal stenosis

Aqueductal stenosis **(AqS)** produces what is sometimes called **triventricular hydrocephalus**, characterized by a normal sized 4th ventricle and enlarged third and lateral ventricles on MRI or CT. Most cases occur in children, however some present for the first time in adulthood.

Etiologies

1. a congenital malformation: may be associated with Chiari malformation or neurofibromatosis
2. acquired
   A. due to inflammation (following hemorrhage or infection, e.g. syphilis, T.B.)
   B. neoplasm: especially brainstem astrocytomas (including tectal gliomas, *see page 608*), lipomas
   C. quadrigeminal plate arachnoid cysts

In infancy

AqS is a frequent cause of congenital hydrocephalus **(HCP)** (up to 70% of cases[60]), but occasionally may be the <u>result</u> of HCP. Patients with congenital AqS usually have HCP at birth or develop it within ≈ 2-3 mos. Congenital AqS may be due to an X-linked recessive gene[61]. Four types of congenital AqS described by Russell (summarized[95]):

1. forking: multiple channels (often narrowed) with normal epithelial lining that do not meet, separated by normal nervous tissue. Usually associated with other congenital abnormalities (spina bifida, myelomeningocele)
2. periaqueductal gliosis: luminal narrowing due to subependymal astrocytic proliferation
3. true stenosis: aqueduct histologically normal
4. septum

In adulthood

AqS may be an overlooked cause of “normal pressure hydrocephalus” in the

adult[96]. It is unknown why some cases of AqS would remain occult, and manifest only in adult-hood. In one series of 55 cases[97], 35% had duration of symptoms < 1 year, 47% for 1-5 years; the longest was 40 yrs. Although most follow this longstanding benign course, there are reports of elevated ICP and sudden death.

Symptoms

See *Table 8-13*. Headache was the most common symptom, and had characteristics of H/A associated with elevated ICP. Visual changes were next, and usually consisted of blurring or loss of acuity. Endocrine changes included menstrual irregularities, hypothyroidism, and hirsutism.

Signs

Papilledema was the most common finding (53%). Visual fields were normal in 78%, the remainder having reduced peripheral vision, increased blind spots, quadrantic or hemianopic field cuts, or scotomata. Intellectual impairment was present in at least 36%. Other signs included: ataxia (29%), "pyramidal tract signs" in 44% (mild hemi- or paraparesis (22%), spasticity (22%), or Babinski's (20%)), anosmia (9%).

EVALUATION

MRI is the test of choice. MRI will show the absence of the normal flow void in the Sylvian aqueduct. Contrast should be given to rule-out tumor.

Table 8-13 Symptoms of aqueductal stenosis presenting in adulthood (55 patients > 16 years age[97])

Symptom	No.	%
H/A	32	58%
visual disturbances	22	40%
mental deterioration	17	31%
gait disturbance	16	29%
frequent falling	13	24%
endocrine disturbance	10	18%
nausea/vomiting	9	16%
seizures	8	15%
incontinence	7	13%

vertigo	6	11%
LE weakness	4	7%
hemiparesis or hemianesthesia	4	7%
diplopia	3	5%
dysarthria	1	
deafness	1	

TREATMENT *(OF NON-TUMORAL AQS)*

Although treatments of the primary lesion have been attempted (e.g. lysis of aqueductal septum), this has fallen into disfavor with the improved efficacy of CSF shunting. CSF is usually shunted to the peritoneum or the vascular system, however shunting to subarachnoid space is also feasible (once obstruction at the level of the arachnoid granulations has been ruled out). A Torkildsen shunt may work in adult cases[95], however pediatric patients with obstructive hydrocephalus may not have an adequately developed subarachnoid space for this to function properly.

Follow-up of at least two years to rule-out tumor is recommended.

8.9. Neural tube defects

CLASSIFICATION

Various classification systems exist, this one is adapted from Lemire[98].

1. neurulation defects: non-closure of the neural tube results in open lesions
   A. craniorachischisis: total dysraphism. Many die as spontaneous abortion
   B. **anencephaly**: AKA exencephaly. Due to failure of fusion of the anterior neuropore. Neither cranial vault nor scalp covers the partially destroyed brain. Uniformly fatal. Risk of recurrence in future pregnancies: 3%
   C. meningomyelocele: most common in lumbar region
      1. myelomeningocele **(MM)**: *see page 248*
      2. myelocele
2. postneurulation defects: produces skin-covered (AKA closed) lesions (some may also be considered “migration abnormalities”, *see below*)
   A. cranial

1. microcephaly: *see below*
2. **hydranencephaly**: loss of most of cerebral hemispheres, replaced by CSF (*see below*). Must R/O maximal hydrocephalus (*see below*)
3. holoprosencephaly: *see below*
4. **lissencephaly**: *see below*
5. porencephaly: *see below* to distinguish from schizencephaly
6. agenesis of corpus callosum: *see below*
7. cerebellar hypoplasia/Dandy Walker syndrome: *see page 240*
8. macroencephaly AKA megalencephaly: *see below*

B. spinal
1. diastematomyelia, diplomyelia: see *Split cord malformation*, page 256
2. hydromyelia/syringomyelia: *see page 510*

Migration abnormalities

A slightly different classification scheme defines the following as abnormalities of neuronal migration (some are considered postneurulation defects, *see above*):

1. **lissencephaly**: The most severe neuronal migration abnormality. Maldevelopment of cerebral convolutions (probably an arrest of cortical development at an early fetal age). Infants are severely retarded and usually don't survive > 2 yrs
   A. **agyria**: completely smooth surface
   B. **pachygyria**: few broad & flat gyri with shallow sulci
   C. **polymicrogyria**: small gyri with shallow sulci. May be difficult to diagnose by CT/MRI, and may be confused with pachygyria
2. **heterotopia**: abnormal foci of (nonenhancing) gray matter which may be located anywhere from the subcortical white matter to (most commonly) the subependymal lining of the ventricles. May manifest as nodules or as a band of cortex. An early migration defect that results from arrest of radial migration. Almost always presents with seizures
3. cortical dysplasia: a cleft that does <u>not</u> communicate with the ventricle. Heterotopias are common. A migration abnormality not quite as severe as schizencephaly
4. **schizencephaly**:
   A. sine qua non: cleft that communicates with the ventricle (communication may be confirmed with CT cisternogram if necessary)

B. cleft lined with cortical grey matter (often abnormal, may have polymicrogyria). This distinguishes it from **porencephaly**, a cystic lesion lined with connective or glial tissue that may communicate with the ventricular system, often caused by vascular infarcts or following intracerebral hemorrhage or penetrating trauma (including repeated ventricular punctures)

C. two forms:
   1. open lipped: large cleft to ventricle. Very severe forms may mimic hydranencephaly (*see below*)
   2. close lipped (walls fused): ★ look for a dimple in the lateral wall of the lateral ventricle immediately under the cortical cleft (the appearance of which may mimic an enlarged sulcus)

D. may be unilateral or bilateral

E. pia and arachnoid fuse

F. there may be an "abnormal" vein that represents a cortical vein that now looks medullary because it follows the cortex into the cleft)

G. absence of septum pellucidum in 80-90%

H. presentation may range from seizures to hemiparesis depending on size and location

Hydranencephaly

A post-neurulation defect. Total or near-total absence of the cerebrum (small bands of cerebrum may be consistent with the diagnosis[99]), with intact cranial vault and meninges, the intracranial cavity being filled with CSF. There is usually progressive macrocrania, but head size may be normal (especially at birth), and, occasionally, microcephaly may occur. Facial dysmorphism is rare.

May be due to a variety of causes, the most commonly cited is bilateral ICA infarcts (which results in absence of brain tissue supplied by the anterior and middle cerebral arteries with preservation in the distribution of the PCA). May also be due to infection (congenital or neonatal herpes, toxoplasmosis, equine virus).

Less affected infants may appear normal at birth, but are often hyperirritable and retain primitive reflexes (Moro, grasp, and stepping reflex) beyond 6 mo. They rarely progress beyond spontaneous vowel production and social smiling. Seizures are common.

Differentiation from hydrocephalus: Progressive enlargement of CSF spaces may occur which can mimic severe ("maximal") hydrocephalus **(HCP)**. It is

critical to differentiate the two since true HCP may be treated by shunting which may produce some re-expansion of the cortical mantle. Many means to distinguish hydranencephaly and HCP have been described, including:

1. **EEG**: shows no cortical activity in hydranencephaly (maximal HCP typically produces an abnormal EEG, but background activity will be present throughout the brain[99]) and is one of the best ways to differentiate the two
2. **CT**[99, 100], **MRI** or **ultrasound**: majority of intracranial space is occupied by CSF. Usually do not see frontal lobes or frontal horns of lateral ventricles (there may be remnants of temporal, occipital or subfrontal cortex). A structure consisting of **brainstem nodule** (rounded thalamic masses, hypothalamus) and medial occipital lobes sitting on the tentorium occupies a midline position surrounded by CSF. Posterior fossa structures are grossly intact. The falx is usually intact (unlike alobar holoprosencephaly), and is not thickened, but may be displaced laterally. In HCP, some cortical mantle is usually identifiable
3. **transillumination** of the skull: in a darkened room, a bright light is placed against the surface of the skull. To transilluminate, the patient must be < 9 mos old and the cortical mantle under the light source must be **< 1 cm thick**[61 (p 215)], can also occur if fluid displaces the cortex inward (e.g. subdural effusions). Too insensitive to be very helpful
4. **angiography**: in "classic" cases resulting from bilateral ICA occlusion, no flow through supraclinoid carotids and a normal posterior circulation is expected

Treatment: Shunting may be performed to control head size, but unlike the case with maximal hydrocephalus, there is no restitution of the cerebral mantle.

Holoprosencephaly

AKA **arhinencephaly**. Failure of the telencephalic vesicle to cleave into two cerebral hemispheres. The degree of cleavage failure ranges from the severe alobar (single ventricle, no interhemispheric fissure) to semilobar and lobar (less severe malformations). The olfactory bulbs are usually small and the cingulate gyrus remains fused. Median faciocerebral dysplasia is common, and the degree of severity parallels the extent of the cleavage failure (*see Table 8-14*). 80% are associated with trisomy (primarily trisomy 13, and to a lesser extent trisomy 18). Survival beyond infancy is uncommon, most survivors are severely retarded, a minority are able to function in society. Some develop shunt dependent

hydrocephalus. The risk of holoprosencephaly is increased in subsequent pregnancies of the same couple.

Table 8-14 The five facies of severe holoprosencephaly[101]

Type of face	Facial features	Cranium and brain findings
cyclopia	single eye or partially divided eye in single orbit; arhinia with proboscis	microcephaly; alobar holoprosencephaly
ethmocephaly	extreme orbital hypotelorism; separate orbits; arhinia with proboscis	microcephaly; alobar holoprosencephaly
cebocephaly	orbital hypotelorism; proboscis-like nose; no median cleft lip	microcephaly; usually has alobar holoprosencephaly
with median cleft lip	orbital hypotelorism; flat nose	microcephaly; sometimes has trigonocephaly; usually has alobar holoprosencephaly
with median philtrum-premaxilla anlage	orbital hypotelorism; bilateral lateral cleft lip with median process representing philtrumpremaxillary anlage; flat nose	microcephaly; sometimes has trigonocephaly; semilobar or lobar holoprosencephaly

Microcephaly

Definition: head circumference more than 2 standard deviations below the mean for sex and gestational age. Terms that are sometimes used synonymously: microcrania, microcephalus. Not a single entity, many of the conditions in *Table 8-14* may be associated with microcephaly. It may also result from maternal cocaine abuse[102]. It is important to differentiate microcephaly from a small skull resulting from craniosynostosis in which surgical treatment may provide opportunity for improved cerebral development.

Macroencephaly[60] (PP 109)

AKA macrencephaly, AKA megalencephaly (not to be confused with *macrocephaly*, which is enlargement of the skull (*see page 1206*)). Not a single pathologic entity. An enlarged brain which may be due to: hypertrophy of gray matter alone, gray and white matter, presence of additional structures (glial overgrowth, diffuse gliomas, heterotopias, metabolic storage diseases…). May be seen in neurocutaneous syndromes (especially neurofibromatosis).

Brains may weigh up to 1600-2850 grams. IQ may be normal, but developmental delay, retardation, spasticity and hypotonia may occur. Head

circumference is 4-7 cm above mean. The usual signs of hydrocephalus (frontal bossing, bulging fontanelle, "setting sun" sign, scalp vein engorgement) are absent. Imaging studies (CT or MRI) show normal sized ventricles and can be used to rule out extra-axial fluid collections.

RISK FACTORS

1. early administration of folic acid[103-105] (0.4 mg/d if no history of neural tube defects) reduces the incidence of neural tube defects **(NTDs)** (confirm that vitamin B_{12} levels are normal, *see page 1187*)
2. folate antagonists (e.g. carbamazepine) doubles the incidence of MM
3. mothers with 5, 10-methylenetetrahydrofolate reductase (MTHFR) gene poly-morphism → reduced levels of tissue folate[106]
4. use of valproic acid (Depakene®) during pregnancy is associated with a 1-2% risk of NTD[107]
5. maternal heat exposure in the form of hottubs, saunas or fever (but not electric blankets) in the first trimester was associated with an increased risk of NTDs[108]
6. obesity (before and during pregnancy) increases the risk of NTD[109, 110]
7. maternal cocaine abuse may increase the risk of microcephaly, disorders of neuronal migration, neuronal differentiation and myelination[102]

PRENATAL DETECTION OF NEURAL TUBE DEFECTS

Serum alpha-fetoprotein (AFP)

(See *Alpha-fetoprotein* on page 721 for background). A high maternal serum AFP (≥ 2 multiples of the median for the appropriate week of gestation) between 15-20 weeks gestation carries a relative risk of 224 for neural tube defects, and an abnormal value (high or low) was associated with 34% of all major congenital defects[111]. The sensitivity of maternal serum AFP for spina bifida was 91% (10 of 11 cases), it was 100% for 9 cases of anencephaly. However, other series show a lower sensitivity. Closed lumbosacral spine defects, accounting for ≈ 20% of spina bifida patients[112], will probably be missed by serum AFP screening, and may also be missed on ultrasound. Since maternal serum AFP rises during normal pregnancy, an overestimate of gestational age may cause an elevated AFP to be interpreted as normal, and an underestimate may cause a normal level to be interpreted as elevated[113].

Ultrasound

Prenatal ultrasound will detect 90-95% of cases of spina bifida, and thus in cases of elevated AFP, it can help differentiate NTDs from non-neurologic causes of elevated AFP (e.g. omphalocele), and can help to more accurately estimate gestational age.

Amniocentesis

For pregnancies subsequent to a MM, if prenatal ultrasound does not show spinal dysraphism, then amniocentesis is recommended (even if abortion is not considered, it may allow for optimal post-partum care if MM is diagnosed). Amniotic fluid AFP levels are elevated with open neural tube defects, with a peak between weeks 13-15 of pregnancy. Amniocentesis also carries a ≈ 6% risk of fetal loss in this population.

8.9.1. Agenesis of the corpus callosum

A failure of commissuration occurring ≈ 2 weeks after conception. Results in expansion of the third ventricle and separation of the lateral ventricles (which develop dilated occipital horns and atria, and concave medial borders).

The corpus callosum **(CC)** forms from rostrum (genu) to splenium[114], ∴ in agenesis there may be an anterior portion with absence of the posterior segment (the converse occurs infrequently). Absence of the anterior CC with presence of some posterior CC is indicative of some form of holoprosencephaly.

Incidence

1 in 2,000-3,000 neuroradiological examinations.

Associated neuropathologic findings[14]

- porencephaly
- microgyria
- interhemispheric lipomas and lipomas of the corpus callosum (*see page 225*)
- arhinencephaly
- optic atrophy

- colobomas
- hypoplasia of the limbic system
- bundles of Probst: aborted beginnings of corpus callosum, bulge into lateral ventricles
- loss of horizontal orientation of cingulate gyrus
- schizencephaly (*see page 243*)
- anterior and hippocampal commissures may be totally or partially absent[115]
- hydrocephalus
- cysts in the region of the corpus callosum
- spina bifida with or without myelomeningocele
- absence of the septum pellucidum: *see page 247*

Possible presentation

- hydrocephalus
- microcephaly
- seizures (rare)
- precocious puberty
- disconnection syndrome: more likely with acquired CC defect than in congenital

May be an incidental finding, and by itself may have no clinical significance. How-ever, may be occur as part of a more complex clinical syndrome or chromosomal abnormality (e.g. Aicardi syndrome: agenesis of CC, seizures, retardation, patches of retinal pigmentation).

8.10. Absence of the septum pellucidum

Etiologies[81] (p 178)

1. holoprosencephaly: *see page 244*
2. schizencephaly: *see page 243*
3. agenesis of the corpus callosum: *see page 246*
4. Chiari type 2 malformation: *see page 238*
5. basal encephalocele
6. porencephaly/hydranencephaly

7. may occur in severe hydrocephalus: thought to be due to necrosis with resorption
8. septo-optic dysplasia: *see below*

Septo-optic dysplasia[81] (p 175-8), [116]

AKA de Morsier syndrome. Incomplete early morphogenesis of anterior midline structures produces hypoplasia of the optic nerves and possibly optic chiasm (affected patients are blind) and pituitary infundibulum. The septum pellucidum is absent in about half the cases. About half the cases also have schizencephaly (*see page 243*).

Presentation may be due to secondary hypopituitarism manifesting as dwarfism, isolated growth hormone deficiency, or panhypopituitarism. Occasionally hypersecretion of growth hormone, corticotropin or prolactin may occur, and precocious puberty may occur. Most patients are of normal intelligence although retardation may occur. Septo-optic dysplasia may be a less severe form of holoprosencephaly, and occasionally may occur as part of this anomaly (with its attendant poorer prognosis for function or survival, *see page 244*). The ventricles may be normal or dilated. May be seen by the neurosurgeon because of concerns of possible hydrocephalus.

8.11. Spinal dysraphism (spina bifida)

DEFINITIONS[61]

spina bifida occulta	Congenital absence of a spinous process and variable amounts of lamina. No visible exposure of meninges or neural tissue (*see below*).

The following two entities are grouped together under the term **spina bifida aperta** (*aperta* from the Latin for “open”) or **spina bifida cystica**.

meningocele	Congenital defect in vertebral arches with cystic distension of meninges, but no abnormality of neural tissue. One third have some neurologic deficit.
myelomeningocele	Congenital defect in vertebral arches with cystic dilatation of meninges and structural or functional abnormality of spinal cord or cauda equina (*see below*).

SPINA BIFIDA OCCULTA (SBO)

Reported prevalence range of SBO: 5-30% of North Americans (5-10% is probably more realistic). The defect may be palpable, and there may be overlying cutaneous manifestations (see *cutaneous stigmata of dysraphism* in *Table 8-17*, page 255).

Often an incidental finding, usually of no clinical importance when it occurs alone. Numerous reviews have shown no statistical association of SBO with nonspecific LBP[117, 118]. An increased incidence of disc herniation was shown in one study[119].

SBO may occasionally be associated with diastematomyelia, tethered cord, lipoma, or dermoid tumor. When symptomatic from one of these associated conditions, the presentation is usually that of tethered cord (gait disturbance, leg weakness and atrophy, urinary disturbance, foot deformities…, see *Tethered cord syndrome*, page 254).

MYELOMENINGOCELE

EMBRYOLOGY

The anterior neuropore closes at gestation day 25. The caudal neuropore closes at day 28.

EPIDEMIOLOGY/GENETICS

Incidence of spina bifida with meningocele or myelomeningocele **(MM)** is 1-2/1000 live births (0.1-0.2%). Risk increases to 2-3% if there is one previous birth with MM, and 6-8% after two affected children. The risk is also increased in families where close relatives (e.g. siblings) have given birth to MM children, especially when on the mother's side of the family. Incidence may increase in times of war, famine or economic disasters, but it may be gradually declining overall[120]. Transmission follows non-Mendelian genetics, and is probably multifactorial. Prenatal folate (in the form of folic acid) lowers the incidence of MM (*see page 245*).

Hydrocephalus in myelomeningocele

Hydrocephalus **(HCP)** develops in 65-85% of patients with MM, and 5-10% of MM patients have clinically overt HCP at birth[121]. Over 80% of MM patients who will develop HCP do so before age 6 mos. Most MM patients will have an associated Chiari type 2 malformation (see *Type 2 (Arnold)-Chiari malformation*, page 238). Closure of the MM defect may convert a latent HCP to

active HCP by eliminating a route of egress of CSF.

Latex allergy in myelomeningocele

Up to 73% of MM patients are allergic to proteins present in latex (the milky sap from the rubber tree Hevea brasiliensis), found only in naturally occurring rubber products (and which are not present in synthetics such as: silicone, vinyl, plastic, neoprene, nitrile…). The allergy is thought to arise from early and frequent exposure to latex products during medical care for these patients, and there is a suggestion that latex-free surgery on these infants may reduce the risk of the development of latex allergy[122].

PRENATAL DIAGNOSIS

See *Prenatal detection of neural tube defects* on page 245.

MANAGEMENT

Intrauterine closure of MM defect

Controversial. Does reduce incidence of Chiari II defect, but it has not been determined if this is clinically significant. Argued whether this reduces incidence of hydrocephalus. Does not improve distal neurologic function.

ADMISSION

1. assessment and management of lesion:
   - A. measure size of defect
   - B. assess whether lesion is ruptured or unruptured
     1. ruptured: start antibiotics (e.g. nafcillin and gentamicin; D/C 6 hrs after MM closure, or continue if shunt anticipated in next 5 or 6 days)
     2. unruptured: no antibiotics necessary
   - C. cover lesion with telfa, then sponges soaked in lactated ringers or normal saline (form a sterile gauze ring around the lesion if it is cystic and protruding) to prevent desiccation
   - D. Trendelenburg position, patient on stomach (keeps pressure off lesion)
   - E. perform surgical closure within 36 hrs unless there is a contraindication to surgery (simultaneous shunt is not usually done except if overt hydrocephalus **(HCP)** at birth): see *Timing of MM*

closure below

2. neurological assessment and management:
   A. items related to spinal lesion
      1. watch for spontaneous movement of the LEs (good spontaneous movement correlates with better later functional outcome[123])
      2. assess lowest level of neurologic function (*see Table 8-15*) by checking response of LEs to painful stimulus: although some infants will have a clear demarcation between normal and abnormal levels, at least 50% show some mixture of normal, reflex, and autonomous activity (arising from uninhibited anterior horn motor neurons)[123]
         a. differentiating reflex movement from voluntary may be difficult. In general, voluntary movement is not stereotyped with repetitive stimulus and reflex movement usually only persists as long as the noxious stimulus is applied

Table 8-15 Findings in various levels of MM lesion[124]

Paralysis below	Findings
T12	complete paralysis of all muscles in LEs
L1	weak to moderate hip flexion, palpable contraction in sartorius
L2	strong hip flexion and moderate hip adduction
L3	normal hip adduction & almost normal knee extension
L4	normal hip adduction, knee extension & dorsiflexion/inversion of foot; some hip abduction in flexion
L5	normal adduction, flexion & lateral rotation of hip; moderate abduction; normal knee extension, moderate flexion; normal foot dorsiflexion; hip extension absent; • produces dorsiflexed foot and flexed thigh
S1	normal hip flexion & abduction/adduction, moderate extension and lateral rotation; strong knee flexion & inversion/eversion of foot; moderate plantarflexion of foot; extension of all toes, but flexion only of terminal phalanx of great toe; normal medial & lateral hip rotation; complete paralysis of foot intrinsic (except abductor and flexor hallucis brevis); • produces clawing of toes and flattening of sole of foot
S2	difficult to detect abnormality clinically; • with growth this produces clawing of the toes due to weakness of intrinsic muscles of sole of foot (innervated by S3)

   B. items related to the commonly associated Chiari type 2 malformation:
      1. measure OFC: risk of developing hydrocephalus (*see above*). Use

OFC graphs (*see* *page 312*), and also look for abnormal rate of growth (e.g. > 1 cm/day)
    2. head U/S within ≈ 24 hrs
    3. check for inspiratory stridor, apneic episodes
3. ancillary assessment and management:
    A. evaluation by neonatologist to assess for other abnormalities, especially those that may preclude surgery (e.g. pulmonary immaturity). There is an average incidence of 2-2.5 additional anomalies in MM patients
    B. bladder: start patient on regular urinary catheterizations, obtain urological consultation (non-emergent)
    C. AP & lat spine films: assess scoliosis (baseline)
    D. orthopedic consultation for severe kyphotic or scoliotic spine deformities and for hip or knee deformities

SURGICAL CONSIDERATIONS

TIMING OF MM CLOSURE

Early closure of MM defect is not associated with improvement of neurologic function, but evidence supports lower infection rate with early closure. MM should be closed within 24 hrs whether or not membrane is intact (after ≈ 36 hrs the back lesion is colonized and there is increased risk of postoperative infection).

Simultaneous MM defect closure and VP shunting

In patients without hydrocephalus, most surgeons wait at least ≈ 3 days after MM repair before shunting. In MM patients with clinically overt HCP at birth (ventriculomegaly with enlarged OFC and/or symptoms), MM repair and shunting may be performed in the same sitting without increased incidence of infection, and with shorter hospitalization[125, 126]. It may also reduce the risk of MM repair breakdown previously seen during the interval before shunting. Patient is positioned prone, head turned to right (to expose the right occiput), right knee and thigh flexed to expose right flank (consider using left flank to prevent confusion with appendectomy scar later in life).

TECHNIQUE

Key concepts of surgical treatment:

- critical goals: 1) free placode from dura (to avoid tethering), 2) water-tight dural closure, 3) skin closure (can be accomplished in essentially all cases). Closure does not restore any neurologic function
- timing goal: surgical closure with latex-free setup ideally ≤ 36 hours after birth
- helpful tips: start at normal dura, open as wide as the defect, trim placode if necessary to close dura, undermine skin to achieve closure (avoid trapping skin -> dermoid tumor)
- post-op CSF leak usually means a shunt is required

General principles[127]: keep the exposed neural tissue moist; prevent desiccation. Use latex-free environment (may reduce development of latex allergy, and reduces maternal antibodies may also cross placenta). Do not allow scrubs or chemical antimicrobials to contact neural placode. Do not use monopolar cautery. At every point during the closure, avoid placing tension on the neural placode.

Multiple layer closure is advocated, 5 layers should be attempted, although occasionally only 2 or so layers may be closed. There is no evidence that multiple layer closure either improves neurologic function or prevents later tethering, but there is a suggestion that when tethering does occur, it may be easier to release when a previous multilayered closure was performed. Silastic does not prevent adherence in series with long follow-up (> 6 yrs), and may even render untethering procedures more difficult.

Begin by dividing the abnormal epithelial covering from the normal skin. The piaarachnoid may be separated from the neural tissue. The placode is folded into a tube and the piaarachnoid is then approximated around it with 7-0 suture (absorbable suture, e.g. PDS, may make future re-operation easier). It often helps to start with normal dura above, and then work down. The dura can then be isolated around the periphery and followed deep to the spinal canal superiorly. The dura is then also formed into a tube and approximated in a water-tight closure. If the dura cannot be closed, the placode may be judiciously trimmed. The filum terminale should be divided if it can be located. The skin is then mobilized and closed. Dermoid tumors may result from retained skin during the closure, but alternatively dermoids may also be present congenitally[128].

If there is a kyphotic deformity, it is repaired at the same sitting as the MM defect closure. The kyphotic bone is rongeured, and 2-0 Vicryl is used to suture the adjacent bones. Some surgeons use a brace post-op, some do not.

POST-OP MANAGEMENT OF MM REPAIR

1. keep patient off all incisions
2. bladder catheterization regimen
3. daily OFC measurements
4. avoid narcotics (midbrain malformation renders these patient more sensitive to respiratory depression from narcotics)
5. if not shunted
   A. regular head U/S (twice weekly to weekly)
   B. keep patient flat to ↓ CSF pressure on incision
6. if a kyphectomy was done, use of a brace is optional (surgeon preference)

LATE PROBLEMS/ISSUES

Include:

1. hydrocephalus: may mimic ≈ anything listed below. ALWAYS RULE OUT SHUNT MALFUNCTION when a MM patient deteriorates
2. syringomyelia (and/or syringobulbia): *see page 510*
3. tethered cord (see *Tethered cord syndrome*, page 254): as many as 70% of MM patients have a tethered cord radiographically (some quote 10-20%), but only a minority are symptomatic. Unfortunately there is no good test to check for symptomatic retethering (SSEPs may deteriorate[129], myelography may help)
   A. scoliosis: early untethering of cord may improve scoliosis (see *Scoliosis in tethered cord*, page 255)
   B. symptomatic tethering may manifest as delayed neurological deterioration[130]
4. dermoid tumor at the MM site[131]: incidence ≈ 16% (*see page 729*)
5. medullary compression at foramen magnum (symptomatic Chiari II malformation, *see page 238*)
6. use of growth hormone to increase stature is controversial

OUTCOME

Without any treatment, only 14-30% of MM infants survive infancy; these usually represent the least severely involved; 70% will have normal IQ's. 50% are ambulatory.

With modern treatment, ≈ 85% of MM infants survive. The most common cause of early mortality are complications from the Chiari malformation (respiratory arrest, aspiration…), where late mortality is usually due to shunt

malfunction. 80% will have normal IQ. Mental retardation is most closely linked to shunt infection. 40-85% are ambulatory with bracing, however, most choose to use wheelchairs for ease. 3-10% have normal urinary continence, but most may be able to remain dry with intermittent catheterization.

LIPOMYELOSCHISIS

Dorsal spinal dysraphism with lipoma. Six forms are described[132], the following 3 are clinically important as possible causes of progressive neurologic dysfunction via tethering (see *Tethered cord syndrome*, page 254) and/or compression:

1. (intra)dural lipoma
2. lipomyelomeningocele (*see below*)
3. fibrolipoma of the filum terminale

LIPOMYELOMENINGOCELE

A subcutaneous lipoma that passes through a midline defect in the lumbodorsal fascia, vertebral neural arch, and dura, and merges with an abnormally low tethered cord[132]. These may be terminal, dorsal, or transitional (between the two).

The intradural fatty tumor may also be known as **lipoma of the cauda equina**. In addition to being abnormally low, the conus medullaris is split in the midline dorsally usually at the same level as the bifid spine, and this dorsal myeloschisis may extend superiorly under intact spinal arches[133]. There is a thick fibrovascular band that joins the lamina of the most cephalic vertebrae with the bifid lamina. This band constricts the meningocele sac and neural tissue, causing a kink in the superior surface of the meningocele. Asymptomatic lipomas of the filum terminale occur in 0.2-4%[134, 135] of MRIs.

The dura is dehiscent at the level of the dorsal myeloschisis, and reflects onto the placode. The lipoma passes through this dehiscence to become attached to the dorsal surface of the placode, and may continue cephalad under intact arches with the possibility of extension into the central canal superiorly to levels without dorsal myeloschisis. The lipoma is distinct from the normal epidural fat which is looser and more areolar. The subarachnoid space typically bulges to the side contralateral to the lipoma. These lipomas account for 20% of covered lumbosacral masses.

PRESENTATION

In a pediatric series, 56% presented with a back mass, 32% with bladder problems, and 10% because of foot deformities, paralysis or leg pain[136].

Physical examination

Almost all patients have cutaneous stigmata of the associated spina bifida: fatty subcutaneous pads (located over the midline and usually extends asymmetrically to one side) with or without dimples, port-wine stains, abnormal hair, dermal sinus opening, or skin appendages[137]. Clubbing of the feet (talipes equinovarus) may occur.

The neurologic exam may be normal in up to 50% of patients (most presenting with skin lesion only). The most common neurologic abnormality was sensory loss in the sacral dermatomes.

Evaluation

Plain LS spine x-rays will show spina bifida in most cases (present in almost all by definition, but some may have segmentation anomalies instead such as butterfly vertebra (*see page 138*)). Abnormalities of fusion and sacral defects may also be seen.

The abnormally low conus can be demonstrated on myelogram/CT or on MRI. MRI also demonstrates the lipomatous mass (high signal on T1WI, low signal on T2WI).

All patients should have pre-op urological evaluation to document any deficit.

Treatment

Since symptoms are due to (1) tethering of the spinal cord, especially during growth spurts, and (2) compression due to progressive deposition of fat, especially during periods of rapid weight gain; the goals of surgery are to release the tethering and reduce the bulk of fatty tumor. Simple cosmetic treatment of the subcutaneous fat pad does not prevent neurologic deficit, and may make later definitive repair more difficult or impossible.

Surgical treatment is indicated when the patient reaches 2 months of age, or at the time of diagnosis if the patient presents later in life. Adjuncts to surgical treatment include evoked potential monitoring and laser. Overall, with surgery, 19% will improve, 75% will be unchanged, and 6% will worsen. Foot deformities often progress regardless.

Surgical technique (modified[133])

1. mobilize the subcutaneous mass, it funnels down through the deep fascia
2. open last intact vertebral arch (work from normal dura)
3. identify the fibrovascular band that crosses the most cephalic widely bifid lamina
4. sectioning the fibrovascular band frees the dural tube and releases the sharp kink in the superior surface of the meningocele
5. taking care to preserve dorsal nerve roots, the dura is incised anterior to the duralipoma junction
6. similar procedure is carried out with arachnoid membrane
7. dural/arachnoid incisions are continued around entire extent of tethered conus
8. cord and placode are untethered (monitoring techniques described in *Tethered cord syndrome* on page 254 are an option)
9. ★ subtotal removal of lipoma: lipoma is then trimmed as completely as possible, intentionally leaving some fat behind to avoid injury to dorsal surface of placode. Superior extension along dorsal surface of cord or into central canal is debulked as much as is safely possible
10. the placode is reformed into a closed neural tube
11. close the pial margins
12. the dura is closed (primarily if possible, or using fascia lata graft if too much tension is placed on folded placode)

DERMAL SINUS

A tract beginning at the skin surface, lined with epithelium. Usually located at either end of neural tube: cephalic or caudal. Most common location is lumbosacral. Probably results from failure of the cutaneous ectoderm to separate from the neuro-ectoderm at the time of closure of the neural groove[61].

SPINAL DERMAL SINUS

May appear as a dimple or as a sinus, with or without hairs, usually very close to midline, with an opening of only 1-2 mm. Surrounding skin may be normal, pigmented ("port wine" discoloration), or distorted by an underlying mass.

The sinus may terminate superficially, may connect with the coccyx, or may traverse between normal vertebrae or through bifid spines to the dural tube. It

may widen at any point along its path to form a cyst; called an **epidermoid cyst** if lined with stratified squamous epithelium and containing only keratin from desquamated epithelium, or called a **dermoid cyst** if also lined with dermis (containing skin appendages, such as hair follicles and sebaceous glands) and also containing sebum and hair.

Although innocuous in appearance, they are a potential pathway for intradural infection which may result in meningitis (sometimes recurrent) and/or intrathecal abscess. Less serious, a local infection may occur. The lining dermis contains normal skin appendages which may result in hair, sebum, desquamated epithelium and cholesterol, within the tract. As a result, the contents of the sinus tract are irritating and can cause a sterile (chemical) meningitis with possible delayed arachnoiditis if it enters the dural space.

Incidence of a presumed sacral sinus (a dimple whose bottom could not be seen on skin retraction): 1.2% of neonates[138].

Dermal sinuses are similar but distinct from **pilonidal cysts** which may also be congenital (although some authors say they are acquired), contain hair, are located superficial to the postsacral fascia, and may become infected.

If the tract expands intrathecally to form a cyst, the mass may present as a tethered cord or as an intradural tumor. Bladder dysfunction is usually the first manifestation.

The tract from a spinal dermal sinus always courses cephalad as it dives inward from the surface. An occipital sinus may penetrate the skull and can communicate with dermoid cysts as deep as the cerebellum or fourth ventricle.

Evaluation

These tracts are NOT to be probed or injected with contrast as this can precipitate infection or sterile meningitis.

Exam is directed towards detecting abnormalities in sphincter function (anal and urinary), lumbosacral reflexes, and lower extremity sensation and function.

Radiologic evaluation

When seen at birth, ultrasound is the best means to evaluate for spina bifida and a possible mass inside the canal.

If seen initially following birth, an MRI should be obtained. Sagittal images may demonstrate the tract and its point of attachment. MRI also optimally demonstrates masses (lipomas, epidermoids…) within the canal.

Plain x-rays and CT are unable to demonstrate the fine tract which may exist between the skin and the dura.

Plain x-rays must be done when embarking on surgery as part of operative planning, as preparation for the possibility of a complete laminectomy.

TREATMENT

Sinuses above the lumbosacral region should be surgically removed. More caudally located sinuses are slightly controversial. Although ≈ 25% of presumed sacral sinuses seen at birth will regress to a deep dimple on follow-up (time not specified), it is recommended that all dermal sinuses should be surgically explored and fully excised prior to the development of neurologic deficit or signs of infection. The results following intradural infection are never as good as when undertaken prior to infection. Surgery within the week of diagnosis is appropriate. Sinuses that terminate on the tip of the coccyx rarely penetrate the dura, and may not need to be treated unless local infection occurs.

Surgical technique

An ellipse is cut around the opening, and the sinus is followed deep until the termination of the tract is encountered. Careful insertion of a lacrimal duct probe under direct vision may facilitate excision without violating the tract. If the tracts penetrates the spine, laminectomy must be performed and the tract followed to its full extent (even if necessary to extend the laminectomy to T12). An extradural cyst may be present. If the tract enters the dura, it usually does so in the midline, and in these cases the dura should be opened and inspected. Extreme care is taken to prevent spilling the contents into the subdural space.

CRANIAL DERMAL SINUS

Stalk begins with a dimple in the occipital or nasal region. Cutaneous stigmata of hemangioma, subcutaneous dermoid cyst, or abnormal hair formation may occur. Occipital sinuses extend caudally, and if they enter the skull, they do so caudal to the torcular herophili. Presentation may include recurrent bacterial (usually *S. aureus*) or aseptic meningitis. Evaluation should include MRI to look for intracranial extension and associated anomalies, including an intracranial dermoid cyst.

Treatment

When operating on a cranial dermal sinus, use a sagittally based incision to permit deep exploration. The tract must be followed completely. Be prepared to enter the posterior fossa.

8.11. Klippel-Feil syndrome

Congenital fusion of two or more cervical vertebrae. Ranges from fusion of only the bodies (congenital **block vertebrae**) to fusion of the entire vertebrae (including posterior elements). Results from failure of normal segmentation of cervical somites between 3-8 weeks gestation. Involved vertebral bodies are often flattened and associated disc spaces are absent or hypoplastic. Hemivertebrae may also occur. Neural foramina are smaller than normal and oval. Cervical stenosis is rare. Complete absence of the posterior elements with an enlarged foramen magnum and fixed hyperextension posture is called **iniencephaly** and is rare. Incidence of Klippel-Feil is unknown due to its rarity and the fact that it is frequently asymptomatic.

Classic clinical triad (all 3 are present in < 50%): low posterior hairline, shortened neck (**brevicollis**), and limitation of neck motion (may not be evident if < 3 vertebrae are fused, if fusion is limited only to the lower cervical levels[139], or if hypermobility of non-fused segments compensates). Limitation of movement is more common in rotation than flexion-extension or lateral bending.

May occur in conjunction with other congenital cervical spine anomalies such as basilar impression and atlanto-occipital fusion. Other clinical associations include scoliosis in 60%, facial asymmetry, torticollis, webbing of the neck (called **pterygium colli** when severe), **Sprengel's deformity** in 25-35% (raised scapula due to failure of the scapula to properly descend from its region of formation high in the neck to its normal position about the same time as the Klippel-Feil lesion occurs), **synkinesis** (mirror motions, primarily of hands but occasionally arms also) and less commonly facial nerve palsy, ptosis, cleft or high arched palate. Systemic congenital abnormalities may also occur including: genitourinary (the most frequent being unilateral absence of a kidney), cardiopulmonary, CNS, and in ≈ 30% deafness[140] (due to defective development of the osseous inner ear).

No symptoms have ever been directly attributed to the fused vertebrae, however symptoms may occur from nonfused segments (less common in short-segment fusions) which may be hypermobile possibly leading to instability or degenerative arthritic changes.

Treatment

Usually directed at detecting and managing the associated systemic anomalies. Patients should have cardiac evaluation (EKG), CXR, and a renal

ultrasound. Serial examinations with lateral flexion-extension lateral C-spine x-rays to monitor for instability. Occasionally, judicious fusion of an unstable nonfused segment may be needed at the risk of further loss of mobility. Also *see page 981*, for recommendations regarding athletic competition.

8.12. Tethered cord syndrome

Abnormally low conus medullaris. Usually associated with a short, thickened filum terminale, or with an intradural lipoma (other lesions, e.g. lipoma extending through dura, or diastematomyelia are considered as separate entities). Most common in myelomeningocele **(MM)**. Diagnosis must be made clinically in MM, as almost all of these patients will have tethering radiographically.

Table 8-16 Presenting signs and symptoms of tethered cord[141] (p 1331-2)

Finding	%
cutaneous findings	54%
hypertrichosis	22%
sub-Q lipoma (no intraspinal extension)	15%
miscellaneous (hemangiomatous discoloration, dermal sinus, multiple manifestations)	17%
gait difficulty with LE weakness	93%
visible muscle atrophy, short limb, or ankle deformity	63%
sensory deficit	70%
bladder dysfunction	40%
bladder dysfunction as only deficit	4%
pain in back, leg, or foot arches	37%
scoliosis or kyphosis*	29%
posterior spina bifida (lumbar or sacral)	98%

* high incidence of scoliosis and kyphosis due to inclusion of series by Hoffman

PRESENTATION

Presenting signs and symptoms in patients with tethered cord are shown in *Table 8-16*.

Myelomeningocele patients

If a MM patient has increasing scoliosis, increasing spasticity, worsening gait (in those previously ambulatory), or deteriorating urodynamics[142]:

- always make sure that there is a working shunt with normal ICP
- if painful, should be considered tethered cord until proven otherwise
- if painless, should be considered syringomyelia until proven otherwise
- may be due to brainstem compression (symptomatic Chiari II malformation, *see page 238*) requiring posterior fossa decompression

Scoliosis in tethered cord

Progressive scoliosis may be seen in conjunction with tethered cord; early untethering of the cord may result in improvement of scoliosis, however, untethering must be done when the scoliosis is mild. When cases of ≤ 10° scoliosis were untethered, 68% had neurologic improvement and the remaining 32% were stabilized, whereas when scoliosis is severe (≥ 50°) ≈ 16% deteriorated.

Tethered cord in adults

Although most cases of tethered cord present in childhood, cases of adult tethered cord have been reported (≈ 50 published cases as of 1982). For comparison of adult and childhood forms, *see Table 8-17*.

Table 8-17 Comparison of childhood and adult tethered cord syndrome[143]
(from J Neurosurg, D. Pang and J.E. Wilberger, Vol. 57, pp. 40, 1982, with permission)

Finding	Childhood tethered cord	Adult tethered cord
pain	uncommon; usually in back and legs, not peri-anal nor perineal	present in 86%, often peri-anal & perineal; diffuse & bilateral; occasionally shock-like
foot deformities	common early; usually progressive cavovarus deformity (club foot)	not seen
progressive spinal deformity	common; usually progressive scoliosis	uncommon (< 5%)
motor deficits	common; usually gait abnormalities & regression of gait training	usually presents as leg weakness
urological symptoms	common; usually continuous urinary dribbling, delayed toilet training, recurrent UTIs, enuresis	common; usually urinary frequency, urgency, sensation of incomplete emptying, stress incontinence, overflow incontinence

trophic ulcerations	relatively common in LEs	rare
cutaneous stigmata of dysraphism	present in 80-100% (tuft of hair, dimple, capillary angioma (**naevus flammeus**)	present in < 50%
aggravating factors	growth spurts	trauma, maneuvers associated with stretching conus, lumbar spondylosis, disc herniation, spinal stenosis

EVALUATION

Radiographically: low conus medullaris (below L2) and thickened filum terminale (definition of thickened filum: normal diameter < 1 mm; diameters > 2 mm are pathological). NB: apparent filum diameter on CT-myelogram may vary with concentration of contrast material.

It is difficult to differentiate a tethered cord from a congenitally low lying conus (filum diameter is generally normal in the latter).

Pre-op evaluation

Pre-operative cystometrogram is strongly recommended, especially if the patient seems continent (postoperative changes in bladder function are not uncommon, possibly due to stretching of the lower fibers of the cauda equina).

TREATMENT

If the only abnormality is a thickened, shortened filum, then a limited lumbosacral laminectomy may suffice, with division of the filum once identified.

If a lipoma is found, it may be removed with the filum if it separates easily from neural tissues.

Distinguishing features of the filum terminale intraoperatively

The filum is differentiated from nerve roots by presence of characteristic squiggly vessel on surface of filum. Also, under the microscope, the filum has a distinctively whiter appearance than the nerve roots, and ligamentous-like strands can be seen running through it. NB: intra-op electrical stimulation and recording of anal sphincter EMG are more definitive.

OUTCOME

In MM, it is usually impossible to permanently untether a cord, however, in a growing MM child, it may be that after 2-4 untetherings that the child will be finished growing and tethering may cease to be a problem. Cases that are untethered early in childhood may recur later, especially during the adolescent growth-spurt. Incidence of post-op CSF leak: 15%.

Adult form: surgical release is usually good for pain relief. However, it is poor for return of bladder function.

8.13. Split cord malformation

There is no uniformly accepted nomenclature for malformations characterized by duplicate or split spinal cords. Pang et al.[144] have proposed the following.

The term split cord malformation **(SCM)** should be used for all double spinal cords, all of which appear to have a common embryologic etiology.

Type I SCM

Defined as two hemicords, each with its own central canal and surrounding pia, each within a separate dural tube separated by a dural-sheathed rigid osseocartilaginous (bony) median septum. This has often (but not consistently) been referred to as **diastematomyelia**. There are abnormalities of the spine at the level of the split (absent disc, dorsal hypertrophic bone where the median "spike" attaches)[145]. Two-thirds have overlying skin abnormalities including: nevi, hypertrichosis (tuft of hair), lipomas, dimples or hemangiomas. These patients often have and an orthopedic foot deformity (neurogenic high arches).

Treatment: symptoms are most commonly due to tethering of the cord; and are usually improved by untethering. In addition to untethering, the bony septum must be removed and the dura reconstituted as a single tube (these spines are often very distorted and rotated, therefore start at normal anatomy and work towards defect). ✖ DO NOT cut the tethered filum until after the median septum is removed to avoid having the cord retract up against septum.

Type II SCM

Consists of two hemicords within a single dural tube, separated by a nonrigid fibrous median septum. This has sometimes been referred to as **diplomyelia**.

Each hemicord has nerve roots arising from it. There is usually no spine abnormality at the level of the split, but there is usually spina bifida occulta in the lumbosacral region.

Treatment: consists of untethering the cord at the level of the spina bifida occulta, and occasionally at the level of the split[145].

8.14. Lumbosacral nerve root anomalies

Congenital anomalies of nerve roots are rare. Should be considered in cases of failed back surgery for herniated disc.

Classification system of Cannon et al.[146].

Type 1 anomalies: include **conjoined nerve root** (2 nerve roots arise from a common dural sheath). They separate at various distances from the thecal sac, and exit through the same or separate neural foramina. Neurosurgeons need to be aware of this anomaly to avoid inadvertent injury e.g. during surgery for herniated disc

Type 2 anomalies: 2 nerve roots exit through one foramen. Variants[147]:

A. leaves an unoccupied neural foramen

B. all foramina occupied, but one foramen has 2 nerve roots

Type 3 anomalies: adjacent nerve roots are connected by an anastomosis

8.15. References

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NOTES

9. Neuroendovascular intervention

Neuroendovascular surgery (AKA endovascular neurosurgery), which overlaps with interventional neuroradiology, employs techniques of catheter-based diagnosis and treatments. This chapter addresses some general aspects of importance to the management of these patients that are not covered in other sections. For endovascular issues related to specific entities (e.g. aneurysms), see the chapter on that subject (listed below).

CONDITIONS TREATED

Conditions that are sometimes amenable to endovascular techniques include:

1. aneurysms: coiling, stent assisted coiling (*see page 1059*)
2. arteriovenous malformations **(AVMs)**: embolization
   A. pial AVMs: *see page 1098*
   B. dural AVMs (considered to be fistulas by some): *see page 1109*
   C. spinal AVMs: *see page 507*
3. arteriovenous fistulas: CCFs (*see page 1113*)
4. acute embolic stroke: intraarterial clot lysis (*see page 1018*) or mechanical clot disruption/removal (*see page 1018*)
5. cerebrovascular arterial dissections: *see page 1160*
6. internal carotid artery stenosis: angioplasty/stenting in high-risk patients (*see page 1151*)
7. tumors: embolization. Primarily used before surgery as an adjunct to decrease vascularity, e.g. with some meningiomas, hemangioblastomas…
8. intracranial atherosclerosis
9. inferior petrosal sinus/cavernous sinus sampling for localizing pituitary microadenomas: *see page 646*

PHARMACOLOGIC AGENTS

Some drugs that are used almost exclusively in endovascular procedures are shown below. Other drugs (e.g. heparin, Plavix®…) are covered in other sections (*see index*).

Platelet glycoprotein IIb/IIIa receptor binding drugs: All are parenteral

eptifibatide (Integrilin®) DRUG INFO

Rx: bolus 180 mcg/kg IV (up to a max of 22.6 mg) over 1-2 minutes followed by infusion of 2 mcg/kg/min (duration of therapy depends on indication - for some up to 96 hrs).

abciximab (ReoPro®) DRUG INFO

Made from the Fab fragment of a monoclonal antibody. Platelet inhibition lasts up to 48 hours.

Rx: bolus with 0.25 mg/kg IV 10-60 minutes prior to procedure (e.g. stenting) followed by infusion of 0.125 mcg/kg/min.

tirofiban (Aggrastat®) DRUG INFO

A synthetic nonpeptide antiplatelet drug. Platelet inhibition lasts 4-8 hours.

Rx: bolus with 0.4 mcg/kg/min IV **x** 30 minutes, followed by infusion of 0.1 mcg/kg/min.

9.1. Neuroendovascular procedure basics

The femoral artery is punctured just below the inguinal ligament (which lies on the line connecting the anterior superior iliac spine and the anterior superior pelvic tubercle) to avoid bleeding at a non-compressible location (which can lead to significant retroperitoneal hematoma). An 18-19 gauge needle is usually employed.

The Seldinger technique is then used to place a wire in the artery with removal of the percutaneous needle and the introduction of the sheath[1].

A guiding catheter is usually used to access the target vessel (carotid or vertebral artery). A microcatheter is inserted co-axially within the guiding catheter to access the lesion (aneurysm, AVM nidus…)

Sheaths and catheters are all kept under pressurized heparinized saline flush. An arterial line flush system may be used.

Systemic anticoagulation with heparin is frequently used during the

procedure and reversal is not always performed.

Femoral Sheath Management

Except as indicated below, the sheath is removed at the end of the procedure. If the patient has not had systemic anticoagulation during the procedure, then manual compression should be performed for 10-20 minutes to achieve hemostasis. This minimizes the risk of local and embolic complications.

If the sheath is to remain in place for an intraoperative examination or a subsequent interventional procedure, then it should remain on heparinized flush. Remove the sheath only when the aPTT has returned to normal (< 36 secs) or when the ACT is < 170.

There are a number of femoral arterial closure devices, including: Starclose, Perclose, Angioseal, Minx…

Stenting

Indications for stent placement:

1. to assist in the coiling of wide necked aneurysms where there is risk of coil herniation into the parent artery. ✖ Stent-assisted coiling is not recommended for ruptured aneurysms because of the need for dual antiplatelet therapy and the increased risk of hemorrhage if EVD placement is required on this regimen[2]
2. treatment of intracranial stenosis due to atherosclerosis
3. cerebrovascular arterial dissections

Initially, only cardiac stents were available, however, they are being replaced by stents which are FDA approved for CNS use and are more suitable[3]. Currently available stents approved for CNS use:

- **Wingspan**: (Boston Scientific, Natick, MA) self-expanding nitinol microstent used for intracranial atherosclerosis, exerts greater outward radial force than stents used for aneurysm coiling
- **Neuroform**: (Boston Scientific, Natick, MA) self-expanding flexible stent used for stent-assisted coiling of wide necked saccular aneurysms
- **Enterprise**: (Cordis Neurovascular, Miami, FL) self-expanding nitinol stent used for stent-assisted coiling of wide necked intracranial aneurysms
- **Pipeline**: (ev[3], Plymouth, MN) self-expanding flow directed bimetallic microstent with braided tubular design that will exclude aneurysms. May also be useful for arterial dissections[4]. Currently awaiting FDA approval

Post stenting medical management

Aspirin is usually recommended indefinitely following stent placement to prevent stent thrombosis. Plavix® is prescribed for at least 6 weeks following stent placement to allow for endothelialization of the stent.

9.2. References

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NOTES

10. Electrodiagnostics

10.1. Electroencephalogram (EEG)

Common EEG rhythms are shown in *Table 10-1*. The primary use of EEG is in the diagnosis and management of seizure disorders. Non-convulsive use of EEG is essentially limited to monitoring for burst suppression (*see below*) (e.g. during carotid endarterectomy) or for differential diagnosis of diffuse encephalopathy, including:

1. differentiating psychogenic unresponsiveness from organic: a normal EEG indicates either psychiatric unresponsiveness or locked-in syndrome
2. non-convulsive status epilepticus (seizures): absence or complex partial status
3. subclinical focal abnormalities: e.g. PLEDs (*see below*), focal slowing…
4. specific patterns diagnostic for certain pathologies: e.g.:
   A. **periodic lateralizing epileptiform discharges (PLEDs)**: may occur with any acute focal cerebral insult (e.g. herpes simplex encephalitis **(HSE)**, abscess, tumor, embolic infarct): seen in 85% of cases of HSE (onset 2-5 d after presentation), if bilateral is ≈ diagnostic of HSE
   B. subacute sclerosing panencephalitis **(SSPE)** (pathognomonic pattern): periodic high voltage with 4-15 secs separation with accompanying body jerks, no change with painful stimulation (differential diagnosis includes PCP overdose)
   C. Creutzfeldt-Jakob disease (*see page 361*): myoclonic jerks. EEG → bilateral sharp wave 1.5-2 per second (early → slowing; later → triphasic). May resemble PLEDs, but are reactive to painful stimulation (most PLEDs are not)
   D. triphasic waves: not really specific. May be seen in hepatic encephalopathy, post-anoxia, and hyponatremia
5. objective measure of severity of encephalopathy: usually used for anoxic encephalopathy (e.g. periodic spikes with seizures indicates < 5% chance of normal neurologic outcome, with high mortality). Alpha coma, burst suppression, and electrocerebral silence are all poor prognosticators

6. differentiating hydranencephaly from severe hydrocephalus (see *Hydranencephaly*, page 244)
7. as a clinical confirmatory test in the determination of brain death (*see page 291*)

Table 10-1 Common EEG rhythms

Rhythm	Symbol	Frequency
delta	Δ	0-3 Hz
theta	θ	4-7 Hz
alpha	α	8-13 Hz
beta	ß	> 13 Hz

BURST SUPPRESSION

Isoelectric intervals interrupted by bursts of 8-12 Hz electrical activity that diminish to 1-4 Hz prior to electrical silence[1]. Often used as an endpoint for titrating neuroprotective drugs such as barbiturates, propofol… (e.g. *see page 1064*).

10.2. Evoked potentials

Evoked potentials are averaged EEG waveforms recorded following repetitive stimulation. The EEGs are then averaged to null-out activity that is not time locked to the stimulus. Resultant waveforms contain peaks that are named N (negative - upward deflection) or P (positive - downward deflection) followed by the latency in milliseconds to the onset of the peak.

Sensory evoked potentials (SEP)

May use electrical stimulation of peripheral nerves (somatosensory or **(SSEP)**), auditory clicks through earphones (auditory or AEP AKA BAER (brainstem auditory evoked response)) or flashing lights through goggles (visual EP or VEP).

Clinical indications for evoked potentials **(EPs)**.

1. diagnosis: (MRI has largely replaced EPs for these 3 indications)

A. vestibular schwannoma
B. subclinical lesions of multiple sclerosis
C. brainstem lesions
2. SSEP (especially from median nerve stimulation) has prognostic significance in cervical spondylotic myelopathy[2]
3. intraoperative use (*see below*)

Brainstem auditory evoked responses (BAER)

AKA auditory brainstem response **(ABR)**, AKA auditory evoked potential **(AEP)**. Auditory clicks are delivered to the patient by earphones. Peaks (*see Table 10-2*).

INTRA-OPERATIVE EVOKED POTENTIALS

For anesthetic requirements for intraoperative SSEP monitoring *see page 4*.

EPs may be used for intraoperative monitoring (e.g. monitoring hearing during resection of vestibular schwannomas, or monitoring SSEPs during some spine surgery), however, their delayed nature often makes them of limited usefulness in avoiding acute intraoperative injury. A 10% increased latency of a major EP peak, or a drop in amplitude ≥ 50% is significant and should cause the surgeon to assess all variables (retractors, instruments, blood pressure…). Intraoperative SSEPs may also be used to localize primary sensory cortex in anesthetized patients (as opposed to using brain mapping techniques in awake patients) by looking for phase reversal potentials across the central sulcus[3, 4] (*see page 150*). For anesthesia requirements for EPs, *see page 4*.

EP monitoring during spine surgery

SSEPs: Typical stimulus sites: median, ulnar, and tibial nerves. Impulses ascend in the ipsilateral posterior column. UE SSEPs travel primarily in the dorsal columns, but LE SSEPs are carried mostly in the dorsolateral fasciculus (*see page 92*) which is supplied by the anterior spinal artery. Thus, UE and LE SSEPs are sensitive to direct mechanical effects primarily on the posterior spinal cord (sensory) and may remain unchanged with some injuries to the anterior cord (motor), LE SSEPs can detect ischemic effects on the anterior cord by virtue of involvement of the anterior spinal artery. Paralytics actually help SSEPs by reducing muscle artifact, but will abolish the visible twitch that confirms that the stimulus is being received.

Criteria for EP changes to trigger notification of surgeon:

1. decrease in peak amplitude > 50%
2. increase in peak latency > 10%
3. complete loss of a waveform

In a personal series of 809 patients[5], 17 had SSEP degradation, 14 of these (82%) responded to intra-op interventions (*see below*), and in 13 of these 14 (93%) there were no new deficits. In the 3 that did not respond, 2 had significant new neurologic deficits.

Transcranial motor evoked potentials (TCMEPs): AKA **motor evoked potentials (MEP):** transcranial electrical or magnetic stimulation of motor cortex and descending motor axons with recording of motor potentials from distal spinal cord or muscle groups. Using direct electrical stimulation is limited in awake patients by local pain. Due to the large potentials, the acquisition time is shorter and feedback to the surgeon is almost immediate. However, due to patient movement from the muscle contractions, continuous recording is usually not possible (except with monitoring the response over the spinal cord). Useful for surgery involving the spinal cord (cervical or thoracic), no utility for lumbar spine. In addition to EP anesthetic requirements, neuromuscular blockade must be minimized to permit ≥ 2 out of 4 twitches. Seizures occur rarely, usually in patients with increased seizure risk and with high-rate stimulation frequency. Contraindications to MEP:

1. history of epilepsy/seizures
2. past surgical skull defects
3. metal in head or neck
4. use special care with implanted electronic devices

Descending evoked potentials (DEP): (Formerly referred to by the misleading term “neurogenic motor evoked potentials”). Rostral stimulation of the spinal cord with recording of a caudal neurogenic response from the spinal cord or peripheral nerve, or a myogenic response from a distal muscle. DEPs can be mediated primarily by sensory nerves and therefore do not represent true motor potentials. However, shown to be sensitive to spinal cord changes and may be useful when TCMEPs cannot be obtained.

Interventions for SSEP deterioration during surgery (options/suggestions):

1. check technical factors:
   A. rule-out 60 Hz. interference from other equipment (O.R. table, C-arm, microscope, anything with a plug)

    B. verify stimulating electrodes are making good contact
    C. check anesthetic technical factors: no paralytics, no acidemia
2. rule-out hypotension or anemia (could contribute to cord ischemia)
3. get an x-ray to rule out change in position
4. release retractors
5. consider repositioning patient, reduce traction, remove shoulder tape…
6. consider giving steroids: some use the methylprednisolone protocol (*see page 936*)
7. remove any hardware that might have caused the change
8. consider "wake up test" (AKA Miami wake-up test): discontinue anesthesia when patient is stable enough to do so and verify if they can move
9. truncate surgery

ABBREVIATIONS

Abbreviations used below: **BAER** = brain stem auditory evoked response; **UE/LE SSEP** = upper/lower extremity somatosensory evoked potential; **PR VER** = pattern reversal visual evoked response which requires patient cooperation and visual attention as opposed to flash VER which may even be done through closed eyelids. See also references[6, 7].

Table 10-2 Evoked potential waveforms
(note: values may differ from lab to lab)

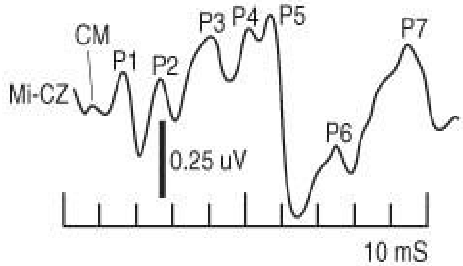
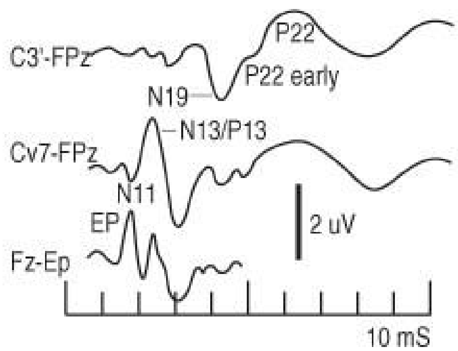
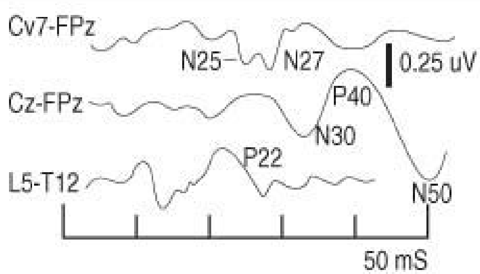
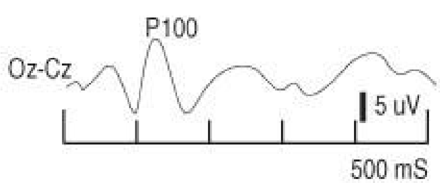
Test	Figure	Possible generators
BAER		CM cochlear microphonic P_1 distal VIII nerve, P_2 proximal VIII or cochlear nucleus, P_3 lower pons (? superior olivary complex), P_4 mid-upper pons, **P_5** upper pons or inferior colliculus
UE SSEP		N_9 (on F_Z-E_P where E_P is Erb's point) AKA EP: entry of volley into distal brachial plexus, N_{11} (on C_{V7}-F_{PZ}): root entry zone (cervical region), N_{13} cervicomedullary junction (recorded from C2), **N_{19}** primary sensory cortex, P_{22} (early) motor cortex, P_{22} (late) IPSP "reaction" to N_{18}
LE SSEP		P_{22} (on L_5-T_{12}): lumbo-sacral plexus, P_{40} (on C_Z-F_{PZ}): sensory cortex (analogous to N18 in UE SSEP, reversed in polarity for ? reason), N_{27} (on C_{V7}-F_{PZ}): ? dorsal column nucleus **N_{30}**
PR VER		P_{100} striate & pre-striate occipital cortex, with contributions from thalamocortical volleys

Table 10-3 Normal values for evoked potentials*
(note: values may differ from lab to lab)

Test	Parameters measured	– – Normal values – –		Comment
		Mean	+2.5 std dev	
BAER	I-V peak latency	4.01 mS	**4.63 mS**	
	I-III peak latency	2.15 mS	**2.66 mS**	prolongation suggests lesion between pons & colliculus, often **vestibular schwannoma**
	V absolute latency	5.7 mS	**6.27 mS**	
	III-V peak latency			prolongation suggests lesion between lower pons & midbrain, may be seen in M.S.
UE SSEP	N_9-N_{18} peak latency	9.38 mS	**11.35 mS**	
LE SSEP	P_{22}-P_{40} peak latency	15.62 mS	**20.82 mS**	
	P_{40} absolute latency	37.20 mS	**44.16 mS**	
PR VER	P_{100} absolute latency		+ 3 S.D.	
	P_{100} inter-eye difference	8-10 mS		Inter-eye difference is more sensitive with full field stimulation. Monocular defect suggests conduction defect in that optic nerve anterior to chiasm (e.g. M.S., glaucoma, compression retinal degeneration). Bilateral defect does not localize.

* normal values in boldface are critical values used as cutoff for abnormal results

10.3. NCS/EMG

Electrodiagnostic studies of peripheral nerves consist of two parts:

1. conduction measurements: typically referred to as "NCV" (nerve conduction velocity) but technically should be called NCS (nerve conduction *studies*) since amplitude, latency and duration of motor & sensory nerves are also evaluated
2. electromyogram **(EMG)** AKA "needle exam" (*see below*)

ELECTROMYOGRAPHY

3 phases of EMG exam:

1. insertional activity: the electric response of the muscle to mechanical irritation caused by small movements of the needle
2. spontaneous activity: in muscle at rest
   A. normal: silent with stationary needle once insertional activity has subsided
   B. **spontaneous activity**: independently produced electrical activity. Usually abnormal (although sometimes seen in normal volunteers).
      1. after <u>denervation</u> (secondary to a nerve injury) or muscle injury:

a. positive sharp waves **(PSW)**

b. **fibrillation potentials** (AKA fibrillations or fibs): action potentials arising from single muscle fibers. Detectable on EMG; not visible to the naked eye (c.f. fasciculations, *see page 787*). Earliest onset 7-10 days after denervation, sometimes not for 3-4 weeks. If the nerve recovers, it may reinnervate the muscle, but with larger motor units resulting in longer duration and decreased numbers

2. myotonic discharges ("dive bomber" sound on speaker monitor)
3. complex repetitive discharge **(CRD)**: ephaptic conduction of groups of adjacent muscle fibers. Occurs in neuropathic or myopathic disorders
4. fasciculation potentials: nonspecific, but typically associated with motor neuron disease (ALS) (*see page 65*)
5. other less common spontaneous activity includes: myokymic, neuromytonic and cramp discharges

3. volitional activity: evaluated with minimal volitional effort and maximal effort

A. motor unit action potential **(MUAP)** analysis: includes evaluation of motor unit amplitude, duration, polyphasia and stability. Generally increase amplitude and duration suggest a disorder of the LMN, and reduction of amplitude and duration suggests a primary myopathic disorder

B. with minimal volitional effort. Two possible abnormal findings

1. reduced recruitment (or fast firing) is always indicative of a neuropathic process
2. early or increased recruitment: indicative of a myopathic process

C. with maximal effort

Definitions

SNAP: sensory nerve action potential. Key concept: since the ganglion of the sensory nerves lies within the neural foramen, preganglionic lesions (injury to the nerve root proximal to the neural foramen, e.g. root compression by herniated disc or root avulsion) does not affect the cell body, and therefore the distal SNAP is unaffected[8]. Postganglionic lesions (distal to the neural foramen, e.g. peripheral nerve injury) reduces SNAP amplitudes and/or slows the sensory conduction velocity.

F-wave: stimulation of a nerve causes orthodromic and antidromic

conduction. Some anterior horn cells that are stimulated antidromically will fire orthodromically producing the F-wave. F-wave latency may be prolonged in multilevel radiculopathy (not sensitive). Most helpful in evaluating proximal root slowing (e.g. GBS - *see page 66*)

H-reflex: practical ≈ only in S1 nerve root, similar information to the ankle jerk. Stimulation of Ia afferent fibers passes through a monosynaptic connection causing an orthodromic alpha-motor action potential that can be measured in the triceps surae.

Volitional activity: the motor unit action potential **(MUAP)** can be assessed only with voluntary muscle contraction by the patient. Components of the MUAP measured include: amplitude, rise time, duration, and number of phases (crossings of the baseline).

Polyphasic potentials: MUAPs with > 4 phases. Normally comprise < 15% of MUAPs. Following a nerve injury, abnormally increased polyphasic potentials can be seen 6-8 weeks after reinnervation begins, gradually increase over several months, and then begin to wane (as firing becomes more synchronous).

Radiculopathy

EMG for evaluating radiculopathy is low yield if the strength exam is normal. ∴ EMG is best reserved for cases with documented weakness where additional localizing/prognostic information is needed, or when the patient's strength cannot be reliably assessed (inability to cooperate, functional overlay…).

EMG is not extremely sensitive for radiculopathy (e.g irritative radiculopathy might not be picked up), this is true in the cervical region more so than in the lumbar region. However, when abnormal, EMG is very specific. If there is no weakness on exam, it is less likely that an EMG will be positive. Findings include spontaneous activity (fibs & PSWs, *see above*) and the earliest possible finding (within 2-3 d) is reduced recruitment with volitional activity, but this occurs only with significant compression of motor fibers.

EMG is useful if there is a concern about possible overlapping peripheral neuropathy (e.g carpal tunnel syndrome vs. C6 radiculopathy).

EMG criteria for radiculopathy

1. fibrillations and/or positive sharp waves in at least 2 muscles innervated

by a single nerve root in question, but by 2 different peripheral nerves
2. abnormal paraspinals: this supports the diagnosis, but is not required since paraspinals will be normal in ≈ 50%

Lumbar radiculopathy from herniated disc

Also *see page 432*. With radiculopathy, SNAP is usually normal (*see above*). Paraspinal muscle fibrillations may occur. Accuracy in predicting level of involvement[9] is ≈ 84%.

Foot drop: the short head of the biceps femoris in the LE is the first muscle innervated by the peroneal division of the sciatic nerve at or just above the popliteal fossa just after the nerve splits off from the sciatic nerve. In cases e.g. of foot drop it is a good muscle to test to determine if there is a peroneal neuropathy vs. a more proximal lesion (i.e. above the popliteal fossa).

Findings with healing radiculopathy (e.g. following discectomy or spontaneous healing):

- motor potentials return first (if nerve injury were "complete", it would take a month to return)
- if lost, sensory potentials return last or may not return
- following laminectomy, paraspinal potentials may no longer be useful because when the muscles are cut during surgery it alters their electrical signals resulting in effective denervation due to muscle injury. Fibs and PSWs decrease in amplitude over time but may remain present indefinitely

Plexopathy

Reduction of SNAP with no paraspinal muscle fibrillations (the dorsal rami exit proximally to innervate the paraspinals, and are involved ≈ only with root lesions).

Nerve root avulsion

Produces muscles weakness and sensory loss with normal SNAP.

10.4. References

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NOTES

11. Neurotoxicology

Also *see* *page 998* for plumbism (lead poisoning) from retained bullets.

11.1. Ethanol

The acute and chronic effects of ethyl alcohol (ethanol, **EtOH**) abuse on the nervous system are protean[1], and are beyond the scope of this text (not to mention the effects of EtOH on other organ systems). Neuromuscular effects include:

1. acute intoxication: *see below*
2. effects of chronic alcohol abuse
   A. **Wernicke's encephalopathy**: *see page 275*
   B. cerebellar degeneration: due to degeneration of Purkinje cells in the cerebellar cortex, predominantly in the anterior superior vermis
   C. central pontine myelinolysis: *see page 11*
   D. stroke: increased risk of
      1. intracerebral hemorrhage: *see page 1121*
      2. ischemic stroke[2]
      3. possibly aneurysmal SAH: *see page 1035*
   E. peripheral neuropathy: *see page 794*
   F. skeletal myopathy
3. effects of alcohol withdrawal: usually seen in habituated drinkers with cessation or reduction of ethanol intake
   A. alcohol withdrawal syndromes: *see below*
   B. seizures: up to 33% of patients have a generalized tonic-clonic seizure 7-30 hrs after cessation of drinking (see *Alcohol withdrawal seizures*, page 399)
   C. delerium tremens **(DTs)**: *see below*

ACUTE INTOXICATION

The primary effect of EtOH on the CNS is depression of neuronal

excitability, impulse conduction, and neurotransmitter release due to direct effects on the cell membranes. *Table 11-1* shows the clinical effects associated with specific EtOH concentrations. **Mellanby effect**: the severity of intoxication is greater when blood alcohol levels are rising than when falling.

In most jurisdictions, individuals with blood ethanol levels ≥ 21.7 mmol/l (100 mg/dl) are defined as legally intoxicated, and a number of states have changed this to 80 mg/dl. However, even levels of 10.2 mmol/l (47 mg/dl) are associated with increased risk of involvement in motor vehicle accidents. Chronic alcoholism leads to increased tolerance; in habituated individuals survival with levels exceeding 1000 mg/dl has been reported.

Table 11-1 Blood ethanol concentrations (in non-alcoholic patients)

[blood EtOH]		Clinical effect
mmol/liter	mg/dl	
5.4	25	mild intoxication: altered mood, impaired cognition, incoordination
> 21.7	100	vestibular and cerebellar dysfunction: increased nystagmus, diplopia, dysarthria, ataxia
> 108.5	500	usually fatal from respiratory depression

ALCOHOL WITHDRAWAL SYNDROME

Compensation for the CNS depressant effects of EtOH occurs in chronic alcoholism. Consequently, rebound CNS hyperactivity may result from falling EtOH levels. Clinical signs of EtOH withdrawal are classified as major or minor (the degree of autonomic hyperactivity and the presence/absence of DTs differentiates these), as well as early (24-48 hrs) or late (> 48 hrs).

Signs/symptoms include: tremulousness, hyperreflexia, insomnia, N/V, autonomic hyperactivity (tachycardia, systolic HTN), agitation, myalgias, mild confusion. If EtOH withdrawal seizures occur, they tend to be early (*see page 399*). Perceptual disturbances or frank **hallucinosis** may also occur early. Hallucinosis consists of visual and/or auditory hallucinations with an otherwise clear sensorium (which distinguishes this from the hallucinations of DTs). DTs can occur 3-4 days after cessation of drinking (*see below*).

Suppressed by benzodiazepines, resumption of drinking, ß-adrenergic antagonists, or α_2-agonists.

PREVENTION OF AND TREATMENT FOR ALCOHOL WITHDRAWAL SYNDROME[3]

Mild EtOH withdrawal is managed with a quiet, supportive environment, reorientation and one-to-one contact. If symptoms progress, institute

pharmacologic treatment.

Benzodiazepines

Benzodiazepines **(BDZs)** are the mainstay of treatment. They reduce autonomic hyperactivity, and may prevent seizures and/or DTs. All BDZs are effective. Initial doses are shown in *Table 11-2* and are higher than those used for treating anxiety. Symptom triggered dosing with repeated evaluation utilizing a standardized protocol (e.g. CIWA-Ar[5]) may be more efficacious than fixed-dose schedules[6]. Avoid IM administration (erratic absorption).

Table 11-2 BDZ doses for EtOH withdrawal*

Drug	Dose	
	Oral	IV
chlordiazepoxide (Librium®)	100 mg initially, then 25-50 mg PO TID-QID, gradually taper over ≈ 4 days). Additional doses may be needed for continuing agitation, up to 50 mg PO hourly[4]	–
lorazepam† (Ativan®)	4 mg initially, then 1-2 mg PO q 4 hrs	1-2 mg q 1-2 hrs
diazepam (Valium®)	20 mg PO initially, then 10 mg PO BID-QID	5-10 mg initially
midazolam (Versed®)		titrate drip to desired effect

* modify as appropriate based on patient response

Adjunctive medications

Associated conditions commonly seen in patients experiencing alcohol withdrawal syndrome include dehydration, fluid and electrolyte disturbances, infection, pancreatitis, and alcoholic ketoacidosis, and should be treated accordingly.

Other medications used for EtOH withdrawal itself include:

1. drugs useful for controlling HTN (caution: these agents should not be used alone because they do not prevent progression to more severe levels of withdrawal, and they may mask symptoms of withdrawal)
   A. ß-blockers: also treat most associated tachyarrhythmias

        1. atenolol (Tenormin®): reduces length of withdrawal and BDZ requirement
        2. ✖ avoid propranolol (psychotoxic reactions)
    B. α-agonists: do not use together with ß-blockers. Clonidine (*see page 21*) has been extensively studied, and can be given in patch form (takes ≈ 2 days)
2. phenobarbital: an alternative to BDZs. Long acting, and helps prophylax against seizures
3. baclofen: a small study[7] found 10 mg PO q d X 30 days resulted in rapid reduction of symptoms after the initial dose and continued abstinence
4. "supportive" medications
    A. thiamine: 100 mg IM q d **x** 3 d (can be given IV if needed, but there is risk of adverse reaction). Rationale: high-concentration glucose may precipitate acute Wernicke's encephalopathy in patients with thiamine deficiency
    B. folate 1 mg IM, IV or PO q d **x** 3 d
    C. $MgSO_4$ 1 gm **x** 1 on admission: helpful only if magnesium levels are low, reduces seizure risk. Be sure renal function is normal before administering
    D. vitamin B_{12} for macrocytic anemia: 100 μg IM (do not give before folate)
    E. multivitamins: of benefit *only* if patient is malnourished
5. seizures: *see page 399* for indications for treatment
    A. phenytoin (Dilantin®): load with 18 mg/kg = 1200 mg/70 kg (*see page 409*)
6. ethanol drip: not widely used. 5% EtOH in D5W, start at 20 cc/hr, and titrate to a blood level of 100-150 mg/dl

DELERIUM TREMENS (DTS)

When DTs occur, they usually begin within 4 days of the onset of EtOH withdrawal, and typically persist for 1-3 days.

Signs and symptoms include: profound disorientation, agitation, tremor, insomnia, hallucinations, severe autonomic instability (tachycardia, HTN, diaphoresis, hyperthermia)[8]. Mortality is 5-10% (higher in elderly), but can be reduced with treatment (including treating associated medical problems and treatment for seizures).

Haloperidol and phenothiazines may control hallucinations, but can lower

the seizure threshold. HTN and tachyarrhythmias should be treated as outline above under alcohol withdrawal syndrome.

WERNICKE'S ENCEPHALOPATHY (WE)

AKA Wernicke-Korsakoff encephalopathy. Classic triad: encephalopathy (consisting of global confusion), ophthalmoplegia, and ataxia (NB: all 3 are present in only 10-33% of cases).

Due to thiamine deficiency. Body stores of thiamine are adequate only for up to ≈ 18 days. May be seen in:

1. a certain susceptible subset of thiamine deficient alcoholics. Thiamine deficiency here is due to a combination of inadequate intake, reduced absorption, decreased hepatic storage, and impaired utilization
2. hyperemesis (as in some pregnancies)
3. starvation: including anorexia nervosa, rapid weight loss
4. gastroplication (bariatric surgery)
5. hemodialysis
6. cancers
7. AIDS
8. prolonged IV hyperalimentation

Oculomotor abnormalities occur in 96% and include: nystagmus (horizontal > vertical), lateral rectus palsy, conjugate-gaze palsies.

Gait ataxia is seen in 87%, and results from a combination of polyneuropathy, cerebellar dysfunction, and vestibular impairment.

Systemic symptoms may include: vomiting, fever.

MRI: May show high signal in T2WI and FLAIR images in the paraventricular (medial) thalamus, the floor of the 4th ventricle, and periaqueductal gray of the midbrain. These changes may resolve with treatment[9]. Atrophy of the mammillary bodies may also be seen. Normal MRI does not R/O the diagnosis.

Treatment

Wernicke's encephalopathy **(WE)** is a medical emergency. When WE is suspected, 100 mg thiamine should be given IM or IV (oral route is unreliable, *see above*) daily for 5 days. ✖ IV glucose can precipitate acute WE in thiamine deficient patients, ∴ give thiamine first.

Thiamine administration improves eye findings within hours to days; ataxia

and confusion improve in days to weeks. Many patients that survive are left with horizontal nystagmus, ataxia, and 80% have **Korsakoff's syndrome** (AKA Korsakoff's psychosis), a disabling memory disturbance involving retrograde and anterograde amnesia.

11.2. Opioids

Includes heroin (which is usually injected IV, but the powder can be snorted or smoked) as well as prescription drugs. Opioids produce small pupils (miosis).

Overdose produces:

1. respiratory depression
2. pulmonary edema
3. coma
4. hypotension and bradycardia
5. seizures may occur with: propoxyphene, meperidine (Demerol®) which may also cause delerium, and the street drug combination of "T's and blues" (*see* *page 397*)
6. fatal overdose may occur with any agent, but is more likely with synthetic opioids such as fentanyl (Sublimaze®) among users unfamiliar with their high potency

Reversal of intoxication[10]

A test dose of naloxone (Narcan®) 0.2 mg IV avoids sudden complete reversal of all opioid effects. If no significant reaction occurs, an additional 1.8 mg (for a total dose of 2 mg) will reverse the toxicity of most opioids. If needed, the dose may be repeated q 2-3 minutes up to a total of 10 mg, although even larger doses may be needed with propoxyphene, pentazocine or buprenorphine (Buprenex®). Naloxone may precipitate narcotic withdrawal symptoms in opioid dependent patients, with anxiety or agitation, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, abdominal cramps, muscle spasms… which are uncomfortable but not life threatening. Clonidine (Catapres®) may be helpful for some narcotic withdrawal symptoms.

With longer acting opioids, especially methadone (Dolophine®), repeat doses of naloxone may be obviated by the use of nalmefene (Revex®), a long-acting narcotic antagonist which is not appropriate for the initial treatment of

opioid overdosage.

11.3. Cocaine

The increasing use of cocaine in its various forms (including crack) is resulting in a rise in the incidence and recognition of its deleterious effects on the CNS. Effects on other body systems (tachycardia, acute myocardial infarction, arrhythmias, rupture of ascending aorta (aortic dissection), abruptio placenta, hyperthermia, intestinal ischemia, sudden death…) are well documented elsewhere, and are not further discussed here.

Cocaine is extracted from *Erythroxylon coca* leaves (and other *Erythroxylon* species) and is thus unrelated to opioids. It blocks the re-uptake of nor-epinephrine by presynaptic adrenergic nerve terminals. It is available in 2 forms: cocaine hydrochloride (heat labile and water soluble, it is usually taken PO, IV or by nasal insufflation) and as the highly purified cocaine alkaloid (free base or crack cocaine, which is heat stable but insoluble in water and is usually smoked).

Peak toxicity occurs 60-90 minutes after ingestion (except for “body packers”), 30-60 minutes after snorting, and minutes after IV injection or smoking (freebase or crack)[10].

Acute pharmacologic effects of cocaine

Acute pharmacologic effects pertinent to the nervous system include:

1. mental status: initial CNS stimulation that first manifests as a sense of well-being and euphoria. Sometimes dysphoric agitation results, occasionally with delerium. Stimulation is followed by depression. Paranoia and toxic psychosis may occur with overdosage or chronic use. Addiction may occur
2. pupillary dilatation (mydriasis)
3. hypertension: from adrenergic stimulation

Non-pharmacologic effects related to the nervous system

1. pituitary degeneration: from chronic intranasal use
2. cerebral vasculitis: less common than with amphetamines

3. seizures: possibly related to the local anesthetic properties of cocaine
4. cerebrovascular accident (CVA, stroke)[11]
    A. intracerebral hemorrhage: see *Intracerebral hemorrhage*, *Etiologies* on page 1119
    B. subarachnoid hemorrhage[12, 13]: possibly as a result of HTN in the presence of aneurysms or AVMs, however, sometimes no lesion is demonstrated on angiography[14]. May possibly be due to cerebral vasculitis
    C. ischemic stroke[15]: may result from vasoconstriction
    D. thrombotic stroke[10]
    E. TIA[16]
5. anterior spinal artery syndrome[16]
6. effects of maternal cocaine use on the fetal nervous system include[17]: microcephaly, disorders of neuronal migration, neuronal differentiation and myelination, cerebral infarction, subarachnoid and intracerebral hemorrhage, and sudden infant death syndrome (SIDS) in the postnatal period

Treatment of toxicity

Most cocaine toxicity is too short-lived to be treated. Anxiety, agitation or seizures may be treated with IV benzodiazepines (e.g. lorazepam, *see page 405*). Refractory HTN may be treated with nitroprusside (*see page 19*) or phentolamine (Regitine®, *see page 681*). IV lidocaine used to treat cardiac arrhythmias may cause seizures[10].

11.4. Amphetamines

Toxicity is similar to that of cocaine (*see above*), but longer in duration (may last up to several hours). Cerebral vasculitis may occur with prolonged abuse (*see page 79*) which may lead to cerebral infarction (*see page 1024*).

Elimination of amphetamines requires adequate urine output. Antipsychotic drugs such as haloperidol (Haldol®) should not be used because of risk of seizures.

11.5. Carbon monoxide

Carbon monoxide **(CO)** is the largest source of death from poisoning in the U.S.A.

Normal cellular function requires ≈ 5 ml O_2/100 ml blood. Blood normally contains ≈ 20 ml O_2/100 ml.

CO binds to hemoglobin **(Hb)** with an affinity ≈ 250 times that of O_2, and it causes a left shift of the Hb/O_2 dissociation curve. It also binds to intracellular myoglobin.

Only ≈ 6% of patients show the classic "cherry-red" color of blood.

Clinical findings

Related to CO-Hb level as shown in *Table 11-3*.

Diagnostic studies

EKG changes are common, usually non-specific ST-T wave changes.

In cases of severe intoxication, CT may show symmetrical low attenuation in the globus pallidus (*see page 1229* for differential diagnosis).

Outcome

Prognosticators

1. outcome is more closely correlated with hypotension than with actual CO-Hb level
2. coma
3. metabolic acidosis
4. EEG
5. CT/MRI changes: in one study, the presence of MRI lesions after 1 month did not accurately predict subsequent outcome
6. CO-Hb level
7. other factors probably have an effect, including: age, severity of exposure

Table 11-3 Levels of CO-Hb

CO-Hb level(%)	Signs/symptoms*
0-10	none

10-20*	mild H/A, mild DOE
20-30	throbbing H/A
30-40	severe H/A, dizziness, dimming of vision, impaired judgement
40-50	confusion, tachypnea, tachycardia, possible syncope
50-60	syncope, seizures, coma
60-70	coma, hypotension, respiratory failure, death
> 70	rapidly fatal

* NB: smokers may have CO-Hb levels of 15% without signs or symptoms

Approximately 40% of patients exposed to significant levels of CO die. 30-40% have transient symptoms but make a full recovery. 10-30% have persistent neurological sequelae including CO-encephalopathy (may be delayed in onset) - impaired memory, irritability, parietal lobe symptoms including various agnosias.

Brain lesions

1. white matter lesions:
    - A. multifocal small necrotic lesions in deep hemispheres
    - B. extensive necrotic zones along lateral ventricles
    - C. Grinker's myelinopathy (not necrosis)
2. grey matter lesions
    - A. bilateral necrosis of globus pallidus
    - B. lesions of hippocampal formation and focal cortical necrosis

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NOTES

12. Coma

12.1. General information

Consciousness has two components: arousal and content. Impairment of arousal can vary from mild (drowsiness or somnolence), to obtundation, to stupor to coma. **Coma** is the severest impairment of arousal, and is defined as the inability to obey commands, speak, or open the eyes to pain.

The Glasgow Coma Scale **(GCS)** is shown in *Table 12-1* (note: the scale is used to assess level of consciousness and is not designed for following neurologic deficits). Some centers record a “T” next to the total score for patients whose verbal axis cannot be assessed because of intubation[2]. 90% of patients with GCS ≤ 8 and none with GCS ≥ 9 meet the above definition of coma. Thus, **GCS ≤ 8** is a generally accepted operational definition of coma.

A scale for use in children is shown in *Table 12-2*[3].

Table 12-1 Glasgow coma* scale[1]
(recommended for age ≥ 4 yrs)

Points†	Best eye opening	Best verbal	Best motor
6	–	–	obeys
5	–	oriented	localizes pain
4	spontaneous	confused	withdraws to pain
3	to speech	inappropriate	flexion (decorticate)
2	to pain‡	incomprehensible	extensor (decerebrate)
1	none	none	none§

* technically, this is a scale of *impaired* consciousness, whereas “coma” implies unresponsiveness

† range of total points: 3 (worst) to 15 (normal)

‡ when testing eye opening to pain, use peripheral stimulus (the grimace associated with central pain may cause eye closure)

§ if no motor response, important to exclude spinal cord transection

Table 12-2 Children's coma scale* (for age < 4 yrs)

Points†	Best eye	Best verbal		Best motor
6	–	–		obeys
5	–	smiles, oriented to sound, follows objects, interacts		localizes pain
		Crying	**Interaction**	
4	spontaneous	consolable	inappropriate	withdraws to pain
3	to speech	inconsistently consolable	moaning	flexion (decorticate)
2	to pain	inconsolable	restless	extensor (decerebrate)
1	none	none	none	none

* same as adult Glasgow coma scale except for verbal response[3]

† range of total points: 3 (worst) to 15 (normal)

Coma results from one or more of the following:

- dysfunction of high brainstem (central upper pons) or midbrain
- bilateral diencephalic dysfunction
- diffuse lesions in both cerebral hemispheres (cortical or subcortical white matter)

Posturing

The following terms are inaccurate in the implication of the location of the lesion. Decorticate posturing implies a more rostral lesion and prognosis may be better.

Decorticate posturing: Classically attributed to disinhibition by removal of corticospinal pathways above the midbrain.

Overview: abnormal flexion in UE and extension in LE.

Detail: slow flexion of arm, wrist and fingers with adduction in the UE. Extension, internal rotation, plantarflexion in LE.

Decerebrate posturing: Classically attributed to disinhibition of vestibulospinal tract (more caudal) and pontine reticular formation **(RF)** by removing inhibition of medullary RF (transection at intercollicular level, between vestibular and red nuclei).

Overview: abnormal extension in UE and LE.

Detail: opisthotonos (head and trunk extended), teeth clenched, arms extended, adducted and hyperpronated (internally rotated), wrists flexed, fingers flexed. Legs extended and internally rotated, feet plantarflexed and inverted, toes plantarflexed.

ETIOLOGIES OF COMA

TOXIC/METABOLIC CAUSES OF COMA

1. electrolyte imbalance: especially hypo- or hypernatremia, hypercalcemia, renal failure with elevated BUN & creatinine, liver failure with elevated ammonia
2. endocrine: hypoglycemia, nonketotic hyperosmolar state, DKA (diabetic ketoacidosis, AKA diabetic coma), myxedema coma, Addisonian crisis (hypoadrenalism)
3. vascular: vasculitis, DIC, hypertensive encephalopathy (*see page 73*)
4. toxic: EtOH, drug overdose (including narcotics, iatrogenic polypharmacy, barbiturates), lead intoxication, carbon monoxide (CO) poisoning, cyclosporine (causes an encephalopathy that shows white-matter changes on MRI that is often reversible with discontinuation of the drug)
5. infectious/inflammatory: meningitis, encephalitis, sepsis, lupus cerebritis, neurosarcoidosis (*see page 71*), toxic-shock syndrome
6. neoplastic: leptomeningeal carcinomatosis, rupture of neoplastic cyst
7. nutritional: Wernicke's encephalopathy, vitamin B_{12} deficiency
8. inherited metabolic disorders: porphyria, lactic acidosis
9. organ failure: uremia, hypoxemia, hepatic encephalopathy, Reye's syndrome, anoxic encephalopathy (e.g. post-resuscitation from cardiac arrest), CO_2 narcosis
10. epileptic: status epilepticus (including non-convulsive status), post-ictal state (especially with unobserved seizure)

STRUCTURAL CAUSES OF COMA

1. vascular:
   A. bilateral cortical or subcortical infarcts (e.g. with cardioembolism due to SBE, mitral stenosis, A-fib, mural thrombus…)
   B. occlusion of vessel supplying both cerebral hemispheres (e.g. severe bilateral carotid stenosis)
   C. bilateral diencephalic infarcts: well described syndrome. May be due to occlusion of a thalamo-perforator supplying both medial thalamic areas or with "top-of-the-basilar" occlusion. Initially resembles metabolic coma (including diffuse slowing on EEG), patient eventually arouses with apathy, memory loss, vertical gaze paresis
2. infectious: abscess with significant mass effect, subdural empyema, herpes simplex encephalitis
3. trauma: hemorrhagic contusions, edema, hematoma (*see below*)

4. neoplastic: primary or metastatic
5. herniation from mass effect: presumably brainstem compression causes dysfunction of reticular activating system or mass in one hemisphere causing compression of the other results in bilateral hemisphere dysfunction
6. increased intracranial pressure: reduces CBF
7. acute lateral shift (midline shift) of the brain: e.g. due hematoma (subdural or epidural): *see Table 12-3*

Table 12-3 Effect of lateral shift on level of consciousness[4]

Amount of midline shift	Level of consciousness
0-3 mm	alert
3-4 mm	drowsy
6-8.5 mm	stuporous
8-13 mm	comatose

PSEUDOCOMA

Differential diagnosis:

1. locked-in syndrome: ventral pontine infarction
2. psychiatric: catatonia, conversion reaction
3. neuromuscular weakness: myasthenia gravis, Guillain-Barré

12.2. Approach to the comatose patient

The following covers nontraumatic coma (see *Head trauma*, page 850 for that topic).

Initial evaluation: includes measures to protect brain (by providing CBF, O_2, and glucose), assesses upper brainstem (Cr. N. VIII), and rapidly identifies surgical emergencies. Keep "pseudocoma" as a possible etiology in back of mind.

APPROACH TO COMATOSE PATIENT, OUTLINE

1. cardiovascular stabilization: establish airway, check circulation (heartbeat,

BP, carotid pulse), CPR if necessary

2. obtain blood for tests
   A. STAT: electrolytes (especially Na, glucose, BUN), CBC + diff, ABG
   B. others as appropriate: toxicology screen (serum & urine), calcium, ammonia, antiepileptic drug **(AED)** levels (if patient is taking AEDs)
3. administer emergency supportive medications
   A. glucose: at least 25 ml of D_{50} IVP. Due to potentially harmful effect of glucose in global ischemia, if possible check fingerstick glucose first, otherwise glucose is given without exception, unless it is known with certainty that serum glucose is normal
   B. naloxone (Narcan®): in case of narcotic overdose. 1 amp (0.4 mg) IVP
   C. flumazenil (Romazicon®): in case of benzodiazepine overdose (*see page 52*). Start with 0.2 mg IV over 30 seconds, wait 30 secs, then give 0.3 mg over 30 secs at 1 minute intervals up to 3 mg or until patient arouses
   D. thiamine: 50-100 mg IVP (3% of Wernicke's present with coma)
4. core neuro exam (assesses midbrain/upper pons, allows emergency measures to be instituted rapidly, more thorough evaluation possible once stabilized): → (see *Core neuro exam* below)
5. if herniation syndrome or signs of expanding p-fossa lesion with brainstem compression (*see Table 12-4*): initiate measures to lower ICP (see *Treatment measures for elevated ICP*, page 876), then get a CT scan if patient begins improving, otherwise emergency surgery (*see page 1021*). ✖ Do <u>NOT</u> do LP

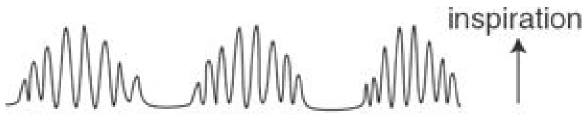
Table 12-4 Signs of herniation syndrome or posterior fossa lesion

HERNIATION SYNDROMES	SIGNS OF P-FOSSA LESION
(also see *Herniation syndromes*, page 284)	(also see *Posterior fossa (infratentorial) tumors*, page 590)
• unilateral sensory or motor deficit • progressive obtundation → coma • unilateral 3rd nerve palsy • decorticate or decerebrate posturing (especially if unilateral)	• initial symptoms of diplopia, vertigo, bilateral limb weakness, ataxia, occipital H/A • rapid onset of deterioration/coma • bilateral motor signs at onset • miosis • absent calorics to horizontal movement, possibly with preserved vertical movements • ocular bobbing • ophthalmoplegia • multiple cranial nerve abnormalities with long tract signs • apneustic, cluster or ataxic respirations

6. if meningitis suspected (altered mental status + fever, meningeal signs…)
   A. if no indication of herniation, p-fossa mass (*see* *Table 12-4*), focal deficit indicating mass effect or papilledema: perform LP, start antibiotics immediately (do not wait for CSF results) (see *Meningitis*, page 343)
   B. if evidence of possible mass effect, coagulopathy or herniation, CT to R/O mass. If significant delay anticipated, consider empiric antibiotics or careful LP with small gauge needle (≤ 22 Ga.), measure opening pressure **(OP)**, remove only a small amount of CSF if OP high, replace CSF if patient deteriorates (LP in this setting may be risky, see *Lumbar puncture*, page 201).
7. treat generalized seizures if present. If status epilepticus is suspected, treat as indicated on page 404 (obtain emergency EEG if available)
8. treat metabolic abnormalities
   A. restore acid-base balance
   B. restore electrolyte imbalance
   C. maintain body temperature
9. obtain as complete history as possible once stabilized
10. administer specific therapies

CORE NEURO EXAM (FOR COMA)

A. **respiratory** rate and pattern: the most common disorder in impaired consciousness
   1. **Cheyne-Stokes**: breathing gradually crescendos in amplitude and then trails off, followed by an expiratory pause, and then the pattern repeats. Hyperpneic phase is usually longer than apneic. Usually seen with diencephalic lesions or bilateral cerebral hemisphere dysfunction (non-specific), e.g. early increased ICP or metabolic abnormality. Results from an increased ventilatory response to CO_2

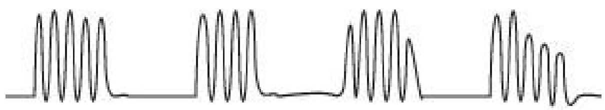


Cheyne-Stokes respiratory pattern

   2. **hyperventilation**: usually in response to hypoxemia, metabolic acidosis, aspiration, or pulmonary edema. True central neurogenic hyperventilation is rare, and usually results from dysfunction within the pons. If no other

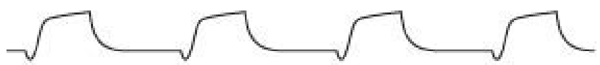
brainstem signs are present, may suggest psychiatric disorder

3. **cluster breathing**: periods of rapid irregular breathing separated by apneic spells, may appear similar to Cheyne-Stokes, may merge with various patterns of gasping respirations. High medulla or lower pons lesion. Often an ominous sign



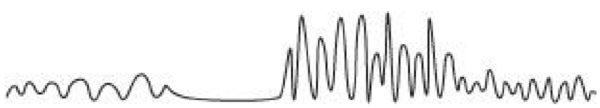
Cluster breathing

4. **apneustic** (rare): a pause at full inspiration. Indicates pontine lesion, e.g. with basilar artery occlusion



Apneustic respiratory pattern

5. **ataxic** (Biot's breathing): no pattern in rate or depth of respirations. Seen with medullary lesion. Usually preterminal



Ataxic respirations

⋆ B. **pupil** (size in mm) in ambient light, and in reaction to direct/consensual light

1. equal and reactive pupils indicates toxic/metabolic cause with few exceptions (*see below*) (may have hippus). The light reflex is the most useful sign in distinguishing metabolic from structural coma
   A. the <u>only</u> metabolic causes of fixed/dilated pupil: glutethimide toxicity, **anoxic encephalopathy**, anticholinergics (including topically applied atropine), occasionally with botulism toxin poisoning
   B. narcotics cause small pupils (<u>miosis</u>) with a small range of constriction and sluggish reaction to light (in severe overdose, the pupils may be so small that a magnifying glass may be needed to see reaction)
2. unequal (note: an afferent pupillary defect does <u>not</u> produce anisocoria (see *Alterations in pupillary diameter*, page 831)):
   A. fixed and dilated pupil: usually due to oculomotor palsy. Possible

herniation, especially if larger pupil associated with ipsilateral 3rd nerve EOM palsy (eye deviated "down and out")

B. possible Horner's syndrome: consider carotid occlusion/dissection

3. bilateral pupil abnormalities

A. pinpoint with minute reaction that can be detected with magnifying glass[5]: pontine lesion (sympathetic input is lost; parasympathetics emerge at Edinger-Westphal nucleus and are unopposed)

B. bilateral fixed and dilated (7-10 mm): subtotal damage to medulla or immeinspiration diate post-anoxia or hypothermia (core temperature < 90° F (32.2° C))

C. midposition (4-6 mm) and fixed: more extensive midbrain lesion, presumably due to interruption of sympathetics and parasympathetics

C. extraocular muscle function

1. deviations of ocular axes at rest

A. bilateral conjugate deviation:

1. frontal lobe lesion (frontal center for contralateral gaze): looks toward side of destructive lesion (away from hemiparesis). Looks away from side of seizure focus (looks at jerking side), may be status epilepticus. Reflex eye movements (*see below*) are normal
2. pontine lesion: eyes look away from lesion and towards hemiparesis; calorics impaired on side of lesion
3. "wrong way gaze": medial thalamic hemorrhage. Eyes look away from lesion and towards hemiparesis (an exception to the axiom that the eyes look towards a destructive supratentorial lesion)[5]
4. downward deviation: may be associated with unreactive pupils (**Parinaud's syndrome**, *see page 114*). Etiologies: thalamic or mid-brain pretectal lesions, metabolic coma (especially barbiturates), may follow a seizure

B. unilateral outward deviation on side of larger pupil (III palsy): uncal herniation

C. unilateral inward deviation: VI (abducens) nerve

D. skew deviation

1. III or IV nerve/nucleus lesion
2. infratentorial lesion (frequently dorsal midbrain)

2. spontaneous eye movements

A. "windshield wiper eyes": random roving conjugate eye movements. Non-localizing. Indicates an intact III nucleus and medial longitudinal fasciculus

B. periodic alternating gaze, AKA "ping-pong gaze": eyes deviate side to side with frequency of ≈ 3-5 per second (pausing 2-3 secs in each direction). Usually indicates bilateral cerebral dysfunction

C. <u>ocular bobbing</u>: repetitive rapid vertical deviation downward with slow return to neutral position. Pontine lesion (*see page 838*)

3. internuclear ophthalmoplegia **(INO)**: due to lesion in medial longitudinal fasciculus **(MLF)** (fibers crossing to contralateral III nucleus are interrupted). Eye ipsilateral to MLF lesion does not adduct on spontaneous eye movement or in response to reflex maneuvers (e.g. calorics) (*see page 834*)
4. reflex eye movements (maneuvers to test brainstem)

A. **oculovestibular reflex**[A], AKA **ice water calorics**: first rule-out TM perforation and occlusion of the EAC by cerumen. Elevate the HOB 30°[B], irrigate one ear with 60-100 ml of ice water[C]. NB: response is inhibited by neuromuscular blocking agents **(NMBA)**

1. a comatose patient with an <u>intact</u> brainstem will have tonic conjugate eye deviation to side of cold stimulus which may be delayed up to one minute or more. There will be no fast component (nystagmus) (the cortical component) even if the brainstem is intact (NB: **oculocephalic reflex**[D] (doll's eyes) provides similar information as oculovestibular reflex[E], but poses a greater risk to the spinal cord if C-spine not cleared)
2. **no response**: symmetrical, could be specific toxin (e.g. neuromuscular block or barbiturates), metabolic cause, brain death or possibly massive infratentorial lesion
3. asymmetric: infratentorial lesion, especially if response inconsistent with 3rd nerve palsy (herniation). Usually maintained in toxic/metabolic coma
4. nystagmus without tonic deviation (i.e. eyes remain in primary position) virtually diagnostic of psychogenic coma
5. contralateral eye fails to adduct: INO (MLF lesion)

B. **optokinetic nystagmus** presence strongly suggests psychogenic coma

D. motor: muscle tone and reflexes, response to pain, Babinski (note asymmetries)

1. appropriate: implies corticospinal tracts and cortex intact
2. asymmetric: supratentorial lesion (tone usually increased), unlikely in metabolic
3. inconsistent/variable: seizures, psychiatric

4. symmetric: metabolic (usually decreased). Asterixis, tremor, myoclonus may be present in metabolic coma
5. hyporeflexia: consider myxedema coma, especially in patient presenting weeks after transsphenoidal surgery
6. patterns
   A. decorticate posturing: arms flex, legs extend: large cortical or subcortical lesion
   B. decerebrate posturing: arms and legs extend: brainstem injury at or below lower midbrain
   C. arms flexed, legs flaccid: pontine tegmentum
   D. arms flaccid, legs appropriate ("man-in-the-barrel syndrome"): anoxic injury (poor prognosis)

E. **ciliospinal reflexes** (pupillary dilatation to noxious cutaneous stimuli): tests integrity of sympathetic pathways
1. bilaterally present: metabolic
2. unilaterally present: possible 3rd nerve lesion (herniation) if on side of larger pupil. Possible pre-existing Horner's syndrome if on side of smaller pupil
3. bilaterally absent: usually not helpful

A. **oculovestibular reflexes** (calorics): the anticipated response is commonly misunderstood. In a normal awake patient there is slow deviation towards the side of the cold stimulus with nystagmus (which is named for the rapid, cortical phase) in the *opposite* direction (hence the mnemonic "COWS" (cold-opposite, warm-same)). Nystagmus will be absent in the comatose patient

B. HOB at 30° places the horizontal semicircular canal **(SCC)** vertically for maximal response[6] (p 56)

C. cold water → downward endolymphatic currents, away from the ampulla of the horizontal SCC[6] (p 57)

D. **oculocephalic reflex** ("doll's eyes" or "doll's head"): do not perform if there is any uncertainty about cervical-spine stability. In an awake patient, the eyes will either move with the head, or, if the movement is slow enough and the patient is fixating on an object, there will be contraversive conjugate eye movement[7] (c.f. oculovestibular reflex which does not depend on patient's level of cooperation). In a comatose patient with an intact brainstem & cranial nerves, there will also be contraversive conjugate eye movement (a positive doll's eyes response)

E. oculovestibular reflexes are absent but oculocephalic are maintained only when vestibular inputs are interrupted, e.g. streptomycin toxicity of labyrinths or bilateral vestibular schwannomas

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12.3. Herniation syndromes

Classic teaching has been that shifts in brain tissue (e.g. caused by masses or increased intracranial pressure) through rigid openings in the skull (herniation) compress other structures of the CNS producing the observed symptoms. This view has been challenged[8], with the hypothesis that herniation may be an epiphenomenon that occurs late in the process and is not actually the cause of the observations. However, herniation models still serve as useful approximations.

The five most common herniation syndromes are:

1. central (transtentorial) herniation (*see page 285*) } supratentorial herniation
2. uncal herniation (*see page 286*) } supratentorial herniation
3. cingulate herniation: cingulate gyrus herniates under falx (AKA subfalcine herniation). Usually asymptomatic unless ACA kinks and occludes causing bifrontal infarction. Usually warns of impending transtentorial herniation
4. upward cerebellar (*see below*) } infratentorial herniation
5. tonsillar herniation (*see below*) } infratentorial herniation

COMA FROM SUPRATENTORIAL MASS[6]

Central and uncal herniation each causes a different form of **rostral-caudal deterioration**. Central herniation results in sequential failure of: diencephalon, midbrain, pons, medulla (*see page 285*). For uncal herniation, *see page 286*. "Classic" signs of increased ICP (HTN, bradycardia, altered respiratory pattern) usually seen with p-fossa lesions may be absent in slowly developing supratentorial masses.

Distinction between central and uncal herniation is difficult when dysfunction reaches the midbrain level or below. Predicting the location of the lesion based on the herniation syndrome is unreliable.

Clinical characteristics differentiating uncal from central herniation

- decreased consciousness occurs early in central herniation, late in uncal
- uncal herniation syndrome rarely gives rise to decorticate posturing

Differential diagnosis of supratentorial etiologies

1. vascular: CVA, intracerebral hemorrhage, SAH
2. inflammatory: cerebral abscess, subdural empyema, herpes simplex encephalitis
3. neoplastic: primary or metastatic
4. traumatic: epidural or subdural hematoma, depressed skull fracture

COMA FROM INFRATENTORIAL MASS

NB: it is essential to identify patients with primary posterior fossa lesions (see *Table 12-4*, page 281) as they may require emergent surgical intervention (*see page 1021*).

Etiologies of infratentorial mass

1. vascular: brainstem infarction (including basilar artery occlusion), cerebellar infarction or hematoma
2. inflammatory: cerebellar abscess, central pontine myelinolysis, brainstem encephalitis
3. neoplasms: primary or metastatic
4. traumatic: epidural or subdural hematoma

HYDROCEPHALUS

Infratentorial masses can produce obstructive hydrocephalus by compressing the Sylvian aqueduct and/or 4th ventricle (*see page 586*).

UPWARD CEREBELLAR HERNIATION

Occasionally seen with p-fossa masses, may be exacerbated by ventriculostomy. Cerebellar vermis ascends above tentorium, compressing the midbrain, and possibly occluding SCAs → cerebellar infarction. May compress sylvian aqueduct → hydrocephalus.

TONSILLAR HERNIATION

Cerebellar tonsils “cone” through foramen magnum, compressing medulla → respiratory arrest. Usually rapidly fatal.

Occurs with either supra- or infratentorial masses or with elevated ICP. May be precipitated by LP. In many cases, there may simply be pressure on the brainstem without actual herniation[9]. There are also cases with significant cerebellar herniation through the foramen magnum with the patient remaining

alert[8].

12.3.1. Central herniation

AKA transtentorial herniation AKA tentorial herniation. Usually more chronic than uncal herniation, e.g. due to tumor, especially of frontal, parietal or occipital lobes.

The diencephalon is gradually forced through the tentorial incisura. The pituitary stalk may be sheared, resulting in diabetes insipidus. PCAs may be trapped along the open edge of the incisura, and may occlude producing cortical blindness (see *Blindness from hydrocephalus*, page 335). The brainstem suffers ischemia from compression and shearing of perforating arteries from basilar artery → hemorrhages within the brainstem (**Duret hemorrhages**).

CT or plain x-ray criteria

Downward displacement of the pineal gland may be demonstrated[10]. Perimesencephalic cisterns are compressed.

DIENCEPHALIC STAGE

Early. May be due to diffuse bilateral hemisphere dysfunction (e.g. from decreased blood flow from increased ICP) or (more likely) from bilateral diencephalic dysfunction due to downward displacement. This stage warns of impending (irreversible) midbrain damage but is frequently reversible if the cause is treated.

Consciousness	Altered alertness is first sign; usually lethargy, agitation in some. Later: stupor → coma.
Respiration	Sighs, yawns, occasional pauses. Later: Cheyne-Stokes.
Pupils	Small (1 - 3 mm), small range of contraction.
Oculomotor	Conjugate or slightly divergent roving eyes; if conjugate then brainstem intact. Usually positive DOLL’S EYES and conjugate ipsilateral response to cold water calorics (CWC). Impaired up-gaze due to compression of superior colliculi and diencephalic pretectum (Parinaud’s syndrome *see page 114*)
Motor	Early: appropriate response to noxious stimuli, bilateral Babinski, gegenhalten (paratonic resistance). If previously hemiparetic contralateral to lesion: may worsen. Later: motionlessness & grasp reflexes, then DECORTICATE (initially contralateral to lesion in most cases).

MIDBRAIN - UPPER PONS STAGE

When midbrain signs fully developed (in adults), prognosis is very poor (extreme ischemia of midbrain). Fewer than 5% of cases will have a good recovery if treatment is successfully undertaken at this stage.

Respiration	Cheyne-Stokes → sustained tachypnea.
Pupils	Moderately dilated midposition (3-5 mm), fixed*.
Oculomotor	Doll's eyes & CWC impaired, may be dysconjugate. MLF lesion → **internuclear ophthalmoplegia** (when doll's or CWC elicited and dysconjugate, medially moving eye moves less than laterally moving eye).
Motor	Decorticate → bilaterally DECEREBRATE (occasionally spontaneously).

* in pontine hemorrhage pinpoint pupils appear because the loss of sympathetics leaves the parasympathetics unopposed, whereas in herniation, the parasympathetics are usually lost, too (3rd nerve injury)

LOWER PONS - UPPER MEDULLARY STAGE

Respiration	Regular, shallow and rapid (20-40/min).
Pupils	Midposition (3-5 mm), fixed.
Oculomotor	Doll's eyes and CWC unelicitable.
Motor	Flaccid. Bilateral Babinski. Occasionally LE flexion to pain.

MEDULLARY STAGE (TERMINAL STAGE)

Respiration	Slow, irregular rate and depth, sighs/gasps. Occasionally hyperpnea alternating with apnea
Pupils	Dilate widely with hypoxia.

OUTCOME AFTER CENTRAL HERNIATION

In a series of 153 patients with signs of central herniation (altered level of consciousness, anisocoria or fixed pupils, abnormal motor findings) 9% had good recovery, 18% had functional outcome, 10% were severely disabled, and 60% died[11].

Factors associated with a better result were young age (especially age ≤ 17 yrs), anisocoria with deteriorating Glasgow Coma Score and nonflaccid motor function. Factors associated with poor outcome were bilaterally fixed pupils, with only 3.5% of these patients having a functional recovery.

12.3.2. Uncal herniation

Usually occurs in rapidly expanding traumatic hematomas, frequently in the lateral middle-fossa or temporal lobe pushing medial uncus and hippocampal gyrus over edge of tentorium, entrapping third nerve and directly compressing midbrain. PCA may be occluded (as with central herniation). For CT criteria *see below*.

Impaired consciousness is NOT a reliable early sign. Earliest consistent sign: unilaterally dilating pupil. However, it is unlikely that a patient undergoing early uncal herniation would be completely neurologically intact except for anisocoria (do not dismiss confusion, agitation, etc.). Once brainstem findings appear, deterioration may be rapid (deep coma may occur within hours).

CT criteria[12]

Tentorial incisura surrounds interpeduncular and pre-pontine cisterns and brainstem. There is great interpersonal variability in the amount of space in the incisura.

Impending uncal or hippocampal herniation may be indicated by encroachment on lateral aspect of suprasellar cistern → flattening of normal pentagonal shape. Once herniation occurs CT may show: brainstem displacement and flattening, compression of contralateral cerebral peduncle, midbrain rotation with slight increase of ipsilateral subarachnoid space. Also, contralateral hydrocephalus may occur[13].

Obliteration of parasellar and interpeduncular cisterns occurs as uncus and/or hippocampus are forced through hiatus. Brainstem compression → AP elongation. Since dural structures enhance with IV contrast, this may be used to help delineate tentorial margins when necessary.

EARLY THIRD NERVE STAGE

(NOT A BRAINSTEM FINDING, DUE TO 3RD NERVE COMPRESSION)

Pupils	Unilaterally dilating pupil (may be sluggish); 85% ipsilateral to lesion[14]
Oculomotor	Doll's = normal or dysconjugate. CWC = slow ipsilateral deviation, impaired nystagmus, may be dysconjugate if external oculomotor ophthalmoplegia **(EOO)**.
Respirations	Normal.
Motor	Appropriate response to nociceptive stimulus. Contralateral Babinski.

LATE THIRD NERVE STAGE

Midbrain dysfunction occurs almost immediately after symptoms extend beyond those due to focal cerebral lesion (i.e. may skip diencephalic stage, due to lateral pressure on midbrain). Treatment delays may result in irreversible damage.

Pupils	Pupil fully dilates.
Oculomotor	Once pupil blown, then external oculomotor ophthalmoplegia (EOO).
Consciousness	Once EOO, stuporous → comatose.
Respirations	Sustained hyperventilation, rarely Cheyne-Stokes.
Motor	Usually produces contralateral weakness. However, the contralateral cerebral peduncle may be compressed against the tentorial edge causing ipsilateral hemiplegia (Kernohan's phenomenon, a false localizing sign). Then bilateral decerebration (decortication unusual).

MIDBRAIN - UPPER PONS STAGE

Pupils	Contralateral pupil fixes in midposition or full dilation. Eventually, both midposition (5-6 mm) and fixed.
Oculomotor	Impaired or absent.
Respirations	Sustained hyperpnea.
Motor	Bilateral decerebrate rigidity.

From this point onward, the uncal syndrome is indistinguishable from central herniation (*see above*).

12.4. Hypoxic coma

Anoxic encephalopathy may be due to **anoxemic anoxia** (drop in pO_2) or **anemic anoxia** (following exsanguination or cardiac arrest). Myoclonus is common.

Vulnerable cells:

1. cerebral grey matter: lesions predominate in 3rd cortical layer (white matter is usually better preserved due to lower O_2 requirements)
2. Ammon's horn is also vulnerable

3. in the basal ganglia **(BG)**:

Table 12-5 Patients with BEST chance of regaining independence*

Time of exam	Finding
< 6 hrs from onset	(pupillary light reflex present) *AND* (GCS-motor > 1) *AND* (spontaneous EOM WNL, i.e. orienting or conjugate roving)
1 day	(GCS-motor > 3) *AND* (GCS-eye improved ≥ 2 from initial)
3 days	(GCS-motor > 3) *AND* (spontaneous EOM WNL)
1 week	GCS-motor = 6
2 weeks	oculocephalic WNL

A. anoxemic anoxia severely affects globus pallidus

B. anemic anoxia affects the caudate nucleus and putamen

4. in the cerebellum: Purkinje cells, dentate nuclei, and inferior olives are affected

Multivariate analysis yields out-come prognosticators shown in *Table 12-5* and *Table 12-6*. NB: this analysis applies only to hypoxic-ischemic coma[15]. More recent studies confirm the poor prognosis of unreactive pupils and lack of motor response to pain[16]; if either of these findings are seen within a few hours after cardiac arrest there is an 80% risk of death or permanent vegetative state, and if present at 3 days these this rate rose to 100%.

Glucocorticoids (steroids) have been shown to have no beneficial effect on survival rate or neurological recovery rate after cardiac arrest[17].

Table 12-6 Patients with virtually NO chance of regaining independence*

Time of exam	Finding
< 6 hrs	no pupillary light reflex
1 day	(GCS-motor < 4) *AND* (spontaneous eye movements not orienting nor conjugate roving)
3 days	GCS-motor < 4
1 week	(GCS-motor < 6) *AND* (at < 6 hrs spontaneous EOM not orienting nor conjugate roving) *AND* (at 3 d GCS-eye < 4)
2 week	(oculocephalic not WNL) *AND* (at 3 d GCS-motor < 6) *AND* (at 3 d GCS-eye < 4)

	AND (at 2 wk GCS-eye not improved at least 2 points from initial)

* abbreviations: WNL = within normal limits, GCS = Glasgow Coma Scale ("GCS-motor" refers to the motor score…); EOM = extraocular muscle;

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13. Brain death

13.1. Brain death in adults

Most states accept some form of “brain death” as a valid determination of death. The President’s Commission provides the following guidelines[1]:

1. the diagnosis of death requires both cessation of function and irreversibility of cessation of either cardiopulmonary system or *entire* brain (including brainstem)
2. for age < 5 years, see *Brain death in children*, page 292
3. with no “complicating conditions” listed below, there are “…no cases of brain functions returning following a 6 hr cessation, documented by clinical examination and confirmatory EEG”[A]
4. with conditions such as massive intracerebral tumor with herniation or gunshot wound to the head, it is possible to pronounce death sooner with more certainty than, e.g. with post cardiac-arrest anoxia or following a coma of unknown etiology
5. when death results from criminal assault, or there is the possibility of litigation regarding the death, extra care must be taken and legal counsel may be advisable before making the determination of brain death

Table 13-1 Summary of findings in brain death (*see text* for details)

1. absence of brainstem reflexes
A. fixed pupils (no response to light)
B. absent corneal reflexes
C. absent oculovestibular reflex (calorics)
D. absent oculocephalic reflex (doll’s eyes)
E. absent gag & cough reflex
2. apnea with arterial $pCO_2 > 60$ mm Hg
3. no response to deep central pain
4. vital signs & general criteria
A. core temp > 32.2° C (90° F)
B. SBP ≥ 90 mm Hg
C. no drugs that could simulate brain death

BRAIN DEATH CRITERIA

Recommendations[1, 2] (*see Table 13-1* for summary):

A. absence of **brainstem reflexes**:

1. ocular examination:
   A. *fixed* pupils: no response to bright light (caution after resuscitation: *see below*). The size of the pupils is unimportant (they are usually midposition (4-6 mm) but may vary to dilated range[B] (9 mm))
   B. absent corneal reflexes[C]
   C. absent oculocephalic (doll's eyes) reflex (contraindicated if C-spine not cleared): *see page 283*
   D. absent **oculovestibular reflex** (cold water **calorics**): instill 60-100 ml ice water into one ear (do not do if TM perforated) with HOB at 30°. Brain death is excluded if <u>any</u> eye movement (*see page 283*). Wait at least 1 minute for response, and ≥ 5 min before testing the opposite side
2. absent oropharyngeal reflex (gag) to stimulation of posterior pharynx
3. no cough response to bronchial suctioning

B. **apnea test** AKA apnea challenge: no spontaneous respirations[D] after disconnection from ventilator (assesses function of medulla). Since elevating $PaCO_2$ increases ICP which could precipitate herniation and vasomotor instability, this test should be reserved for last and only used when the diagnosis of brain death is reasonably certain. Guidelines[4, 5]

1. apnea for > 2 minutes with $PaCO_2 > 60$ mm Hg or $PaCO_2 > 20$ mm Hg over base-line or pH < 7.3 (CO_2 is the most potent stimulus for respirations). If patient does not breathe by this point, they won't breathe at a higher $PaCO_2$. Not valid with severe COPD or CHF
2. to prevent hypoxemia during the test (with the danger of cardiac arrhythmia or myocardial infarction):
   - precede the test with 15 minutes of ventilation with 100% F_IO_2 (preoxygenation)
   - prior to the test, adjust the ventilator to bring the $PaCO_2 \approx 40$ mm Hg (to shorten the test time and thus reduce the risk of hypoxemia)
   - during the test, have passive O_2 flow administered at 6 L/min through either a pediatric oxygen cannula or a No. 14 French tracheal suction catheter (with the side port covered with adhesive tape) passed to the estimated level of the carina

3. starting from normocapnea, the average time to reach $PaCO_2 = 60$ mm Hg is **6 minutes** (classic teaching is that $PaCO_2$ rises 3 mm Hg/min, but in actuality this varies widely, with an average 3.7 ± 2.34; or 5.1 mm Hg/min if starting at normocarbia[5]). Sometimes as long as 12 minutes may be necessary
4. the test is aborted prematurely if:
   • the patient breathes: incompatible with brain death
   • significant hypotension occurs
   • if O_2 saturation drops below 80% (on pulse oximeter)
   • significant cardiac arrhythmias occur
5. if patient does not breathe, send ABG at regular intervals and at the completion of test regardless of reason for termination. If the patient does not breathe for at least 2 minutes after a $PaCO_2 > 60$ mm Hg is documented, then the test is valid and is compatible with brain death (if the patient is stable and ABGs results are available within a few minutes, the apnea challenge may be continued while waiting for results in case the $PaCO_2$ is < 60)
6. if $PaCO_2$ stabilizes below 60 mm Hg and the pO_2 remains adequate, try reducing the passive O_2 flow rate slightly (O_2 flow may be washing out CO_2)

C. no motor function
1. no response to deep central pain
2. true decerebrate or decorticate posturing or seizures are incompatible with the diagnosis of brain death
3. spinal cord mediated reflex movements (including flexor plantar reflexes, flexor withdrawal, muscle stretch reflexes[6], and even abdominal and cremasteric reflexes) can be compatible with brain death, and may occasionally consist of complex movements[7], including bringing one or both arms up to the face[8], or sitting up (the “Lazarus” sign[9]) especially with hypoxemia (thought to be due to spinal cord ischemia stimulating surviving motor neurons in the upper cervical cord). If complex integrated motor movements occur, it is recommended that confirmatory testing be performed prior to pronouncement of brain death[10]

D. absence of complicating conditions (that could simulate brain death on exam):
1. hypothermia: core temp should be > 32.2° C (90° F). Below this temp,

pupils may be fixed and dilated[11], respirations may be difficult to detect, and recovery is possible[12]

2. no evidence of remediable exogenous or endogenous intoxication, including drug or metabolic (barbiturates, benzodiazepines, meprobamate, methaqualone, trichloroethylene, paralytics, hepatic encephalopathy, hyperosmolar coma…). If there is doubt, depending on circumstances, lab tests including drug levels (serum and urine) may be sent. Pseudocholinesterase deficiency is present in 1/3000 patients which can cause succinycholine to last up to 8 hours (instead of 5 mins). A twitch monitor can rule-out NMB (place the electrodes immediately behind the eye or across the zygomatic arch)
3. shock (SBP should be ≥ 90 mm Hg) and anoxia. Loss of > 45% of circulating blood volume can produce lethargy
4. immediately post-resuscitation: shock or anoxia may cause fixed and dilated pupils. Atropine may cause slight dilatation but <u>not</u> unreactivity (*see page 292*). Neuromuscular blockage (e.g. for intubation) does not affect pupils because the iris lacks nicotinic receptors
5. patients coming out of pentobarbital coma (wait until level ≈ ≤ 10 mcg/ml)

E. confirmation of brain death by use of *Clinical confirmatory tests* (EEG, angiography, CRAG, BAER…, *see below*) is not required, but may be used as determined by judgement of attending or consulting physician

F. recommended <u>observation periods</u> during which time the patient fulfills criteria of clinical brain death before the patient may be pronounced dead:
1. in situation where <u>overwhelming</u> brain damage from an irreversible condition is well established (e.g. massive intracerebral hemorrhage), some experts will pronounce death following a single valid brain death exam in conjunction with a clinical confirmatory test
2. if an irreversible condition is well established, and clinical confirmatory tests are used: 6 hours
3. if an irreversible condition is well established and no clinical confirmatory tests are used: 12 hours
4. if diagnosis is uncertain and no clinical confirmatory tests: 12-24 hours
5. if anoxic injury is the cause of brain death: 24 hours (may be shortened if cessation of CBF is demonstrated)

A. note: EEG is <u>not</u> mandatory, see *recommended observation periods…*, page 291

B. cervical sympathetic pathways may remain intact

C. corneal reflex: eye closing to corneal (not scleral) stimulation
D. respirations are defined as abdominal or chest excursions that produce adequate tidal volumes; if there is any question, a spirometer may be connected to the patient[3]

CLINICAL CONFIRMATORY TESTS

CEREBRAL ANGIOGRAPHY

Criteria: absence of intracranial flow at the level of the carotid bifurcation or circle of Willis[2]). Filling of the superior sagittal sinus may occur in a delayed fashion. Interobserver validity has not been studied. Not routinely used in the diagnosis of brain death, but may be employed in difficult situations.

EEG

Can be done at bedside. Requires experienced interpreter. Does not detect brainstem activity, and electrocerebral silence **(ECS)** does not exclude the possibility of reversible coma. Thus, at least 6 hours observation is recommended in conjunction with ECS. Using ECS as a clinical confirmatory test should be done only in patients without drug intoxication, hypothermia, or shock.

Definition of **electrocerebral silence** on EEG: no electrical activity > 2 μV with the following requirements:

- recording from scalp or referential electrode pairs ≥ 10 cm apart
- 8 scalp electrodes and ear lobe reference electrodes
- inter-electrode resistance < 10,000 Ω (or impedance < 6,000 Ω) but over 100 Ω
- sensitivity of 2 μV/mm
- time constants 0.3-0.4 sec for part of recording
- no response to stimuli (pain, noise, light)
- record > 30 mins
- repeat EEG in doubtful cases
- qualified technologist and electroencephalographer with ICU EEG experience
- telephone transmission not permissible

CEREBRAL RADIONUCLIDE ANGIOGRAM (CRAG)

Can be performed at the bedside with a general purpose scintillation camera

with a low energy collimator[A]. May not detect minimal blood flow to the brain, especially brainstem, therefore 6 hours observation in conjunction with CRAG is recommended unless there is a clear etiology of overwhelming brain injury (e.g. massive hemorrhage or GSW).

A. portable scintillation cameras are becoming increasingly scarce

May be useful to confirm clinical brain death in the following settings:

1. where complicating conditions are present, e.g. hypothermia, hypotension (shock), drug intoxication
2. severe facial trauma where ocular findings may be difficult or confusing
3. in patients with severe COPD or CHF where apnea testing may not be valid
4. to shorten the observation period, especially when organ donation is a possibility

Technique

1. scintillation camera is positioned for an AP head and neck view
2. inject 20-30 mCi of ^{99m}Tc-labeled serum albumin or pertechnetate in a volume of 0.5-1.5 ml into a proximal IV port, or a central line, followed by a 30 ml NS flush
3. perform serial dynamic images at 2 second intervals for ≈ 60 seconds
4. then, obtain static images with 400,000 counts in AP and then lateral views at 5, 15 & 30 minutes after injection
5. if a study needs to be repeated because of a previous non-diagnostic study or a previous exam incompatible with brain death, a period of 12 hours should lapse

Findings

No uptake in brain parenchyma = "hollow skull phenomenon" (*see Figure 13-1*). Termination of carotid circulation at the skull base, and lack of uptake in the ACA and MCA distributions (absent "candelabra effect"). There may be delayed or faint visualization of dural venous sinuses even with brain death[13] due to connections between the extracranial circulation and the venous system.

Transcranial doppler[3]

1. small peaks in early systole without diastolic flow or reverberating flow (indicative of significantly increased ICP)
2. initial absence of doppler signals cannot be used as criteria for brain death since 10% of patients do not have temporal insonation windows

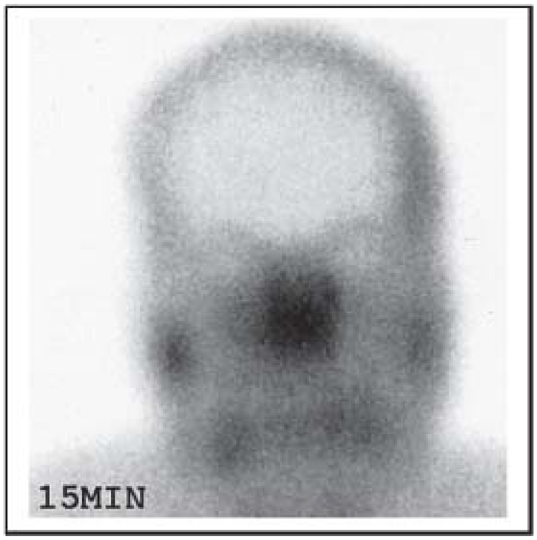

Figure 13-1 "Hollow-skull" sign on CRAG (static AP view taken[15] minutes after injection)

SSEPs

Bilateral absence of N20-P22 response with median nerve stimulation.

Atropine

In brain death, 1 amp of atropine (1 mg) IV should not affect the heart rate due to the absence of vagal tone (the normal response to atropine of increased heart rate rules out brain death, but absence of the response is not helpful since some conditions such as Guillain-Barre may blunt the response).

Systemic atropine in usual doses causes slight pupillary dilatation[14, 15], but does not eliminate reaction to light (therefore, to eliminate uncertainty, it is prudent to examine the pupils before giving the atropine).

13.2. Brain death in children

Criteria for death: irreversible loss of cardiopulmonary or entire brain

function (as in adult), but the (clinically unproven) assumption that a child's brain is more resilient results in more difficult determination of brain death. The following guidelines are proposed for patients < 5 yrs age[16]:

- these recommendations are not applicable for the premature infant
- determination of proximate cause of coma should be made to ensure absence of remediable conditions: especially toxic and metabolic disorders, sedatives, paralytics, hypothermia, hypotension (for age), and surgically treatable conditions
- criteria:
    A. coma and apnea must coexist: including complete loss of consciousness, vocalization and volitional activity
    B. absence of brainstem function
        1. midposition or fully dilated pupils, unresponsive to light (R/O drug effects)
        2. EOM: absence of spontaneous, doll's eyes and caloric movements of eyes
        3. absence of bulbar musculature movement: including oropharyngeal and facial muscles; absence of corneal, gag, cough, suck, and rooting reflex
        4. absence of respiratory movement (usually tested after other criteria met)
        5. flaccid tone and absence of spontaneous or induced movements (spinal myoclonus and spinal cord movements, e.g. reflex withdrawal are not included)
        6. examination results should remain consistent with brain death throughout observation period
- observation periods according to age:
    A. in newborns born at or after term (> 38 wks): 7 days
    B. age 7 days - 2 mos: 2 examinations and 2 EEGs 48 hrs apart (repeat exam unnecessary if cerebral radionuclide angiogram **(CRAG)** fails to visualize cerebral arteries)
    C. age 2-12 mos: 2 examinations and 2 EEGs 24 hrs apart (repeat exam unnecessary if CRAG negative)
    D. age > 12 mos: if irreversible condition exists, laboratory testing is not necessary, and 12 hrs observation is sufficient (unclear conditions, especially hypoxic-ischemic encephalopathy, are difficult to assess, and 24 hrs observation is suggested unless electrocerebral silence on EEG or a negative CRAG confirm diagnosis)

• confirmatory tests:
  A. EEG: standard requirement for 10 cm electrode distance (*see* *page 292*) may be decreased in proportion to size of head
  B. CRAG: applicability to patient < 2 mos age unproven

13.3. Organ and tissue donation

State and federal laws require families of individuals satisfying criteria for brain death to be approached about the possibility of organ donation. Facts that may be conveyed to family in order to help their understanding about organ procurement:

1. any or all suitable organs may be individually specified for donation or to be excluded from consideration for donation
2. organ procurement may be done in such a way as not to interfere with an open casket funeral (i.e. disfigurement can be avoided)
3. families can receive information as to the ultimate use of any recovered organs

13.3.1. Criteria for qualification for organ donation

General exclusionary criteria for organ donation (modified[17])

1. infection
   A. untreated septicemia
   B. the following infections or conditions: AIDS, viral hepatitis, viral encephalitis, Guillain-Barré syndrome
   C. current IV drug abuse
   D. active TB
2. malignancy: brain tumors represent possible exceptions (*see below*)
3. relative exclusions: chronic untreated HTN, hypotension (desired SBP > 100 with normal CVP)
4. disease of the organs considered for donation
5. anencephalic newborns: recent consensus is that the functioning brainstem in these infants (e.g. spontaneous respirations) disqualifies them from the diagnosis of brain death (furthermore, few such organs would likely benefit others)[18]

Guidelines for inclusion (some recommendations from reference[17] **included)**

These guidelines are constantly being revised, in part due to improved results with the use of cyclosporin in recipients. In general, consultation with a transplant coordinator is recommended to determine appropriateness of donation.

1. brain death or cardiac death[19]
2. organs:
   A. **kidneys**: age > 6 mos (because of size). Normal blood pressure, BUN, serum creatinine & U/A. No SLE (because of possible lupus nephritis)
   B. **heart** and **heart/lung**: age ideally < 40 years for males and < 45 for females (above these ages, a cardiac cath is usually performed) but up to 60 yrs may be used depending on condition of heart and potential recipients). Exam by cardiologist indicating no heart disease (cardiomyopathy, valve defect, reduced ejection fraction, severe ASHD, S/P CABG). No IDDM
   C. **liver**: age > 1 mos. Normal hepatic function (normal or acceptable AST, ALT, LDH, bilirubin (direct, indirect & total) and normal clotting studies) with no history of liver disease
   D. **pancreas**: age 15 - 40 yrs. No history of diabetes. Normal serum glucose and amylase
3. tissues:
   A. <u>corneas</u>: age ≥ 1 yr. Neither cancer nor sepsis disqualifies (rabies and Creutzfeldt-Jakob disease are contraindications)
   B. <u>skin</u>: age 15-65 yrs. Excluded if cancer
   C. <u>bone</u>: age 15-65 yrs. Excluded if cancer
   D. <u>bone marrow</u>: age ≤ 50 yrs
   E. <u>heart valves</u>: age ≤ 55 yrs

13.3.2. Organ donation in patients with brain tumors

Among patients with a brain tumor:

1. those that are <u>not</u> candidates for organ donation:
   A. metastatic tumors to the brain
   B. brain tumors that have been manipulated (biopsied or excised)
   C. patients with brain tumors who have been shunted
2. those that might be candidates, but considered *high-risk* donors[A] include

unmanipulated:

A. glioblastoma
B. anaplastic astrocytoma
C. medulloblastoma

3. unmanipulated tumors that might not be considered high risk
   A. hemangioblastoma
   B. meningioma

Optimally, if no metastases are seen on CT (chest, abdomen and pelvis) and no mets are found at time of organ procurement, a brain biopsy would be performed after the organs are procured at the same anesthetic and the organs would not be “released” until the biopsy proves which of the above categories applies.

13.3.3. Management after brain death for organ donation

Note: once brain death occurs, cardiovascular instability eventually ensues, generally within 3-5 days, and management with pressors is usually required. Fluid and electrolyte imbalances from loss of hypothalamic regulation must be normalized. In some instances a beating-heart cadaver can be maintained for months[20].

1. consent: must be obtained from donor’s legal guardian. NB: must also be obtained from medical examiner or coroner’s office for all cases under their jurisdiction (in most states, death resulting from accident, within 24 hrs of hospitalization, etc.)
2. signed note in chart stating date and time patient pronounced brain dead
3. contact transplant coordinator at earliest possible time
4. wean from vasopressors if possible. Control hypotension through volume expansion whenever possible (after brain death, ADH production ceases, producing diabetes insipidus with high urine output, thus copious fluid administration is anticipated (> 250-500 ml/hr is common). Most centers prefer AVOIDING exogenous ADH (vasopressin (Pitressin®)) if possible since the risk of renal shutdown increases in brain-death
   A. start with crystalloid (D5 1/4 NS + 20 mEq KCl/L is generally a good choice since it replaces free water), replace urine cc for cc plus 100 cc/hr maintenance

B. use colloid (FFP, albumin…) if unable to maintain BP by replacement

A. high-risk organs may be considered e.g. for liver transplants in patients who are very low on the list due to age or hepatocellular cancer

C. use vasopressors if still hypotensive. Start with low dose dopamine, increase up to ≈ 10 µg/kg/min, add dobutamine if still hypotensive at this dosage

D. if UO is still > 300 ml/hr after above measures, use ADH analog (aqueous vasopressin (Pitressin®) is preferred over DDAVP to avoid renal shutdown)

5. thyroglobulin given IV converts some cells from anaerobic to aerobic metabolism which may help stave off cardiovascular collapse

LABORATORY EVALUATION[17]

General initial labs

1. serology: VDRL or RPR, HBsAg, HIV, CMV, ABO blood group, HLA tissue type
2. chemistry: electrolytes, glucose, BUN, creatinine, calcium, phosphate, liver function tests, U/A (urine analysis)
3. hematology: CBC, PT/PTT
4. microbiology: blood, urine and sputum cultures; sputum Gram stain

Kidney donor

1. in addition to general labs (*see above*), check BUN & creatinine ≈ q day
2. check electrolytes ≈ q 12 hrs (modify as appropriate)

Liver donor

1. in addition to general labs (*see above*), check LDH, AST, ALT, bilirubin (direct, indirect, and total)

Heart donor

1. all require an echocardiogram prior to donation

13.3.4. Organ donation after cardiac death

Key concepts:

> • candidates: ventilator dependent patients (typically with brain or spinal cord injury) who are so near death that further care is futile
> • consent from legal next of kin for: organ donation, heparin, and femoral lines
> • clearance from medical examiner when applicable (usually unnatural death)
> • counsel the family that the procedure cannot be done in ≈ 20%. They are to be notified immediately if this happens and end-of-life care resumes
> • transplant team cannot participate in end-of-life care, declaration of death, and should not be in O.R. until after cardiad death is declared

Covered in this section because of relevance to organ donation.

Candidates for organ donation after cardiac death are typically ventilator dependent patients with brain or spinal cord injuries who are so near death that further treatment is futile, but who do not meet brain death criteria. Organs typically recovered in this manner: kidneys, liver, pancreas, lungs, and rarely the heart[19].

Ethical concerns related to this practice have been raised[21].

Cardiology consultation may help determine the likelihood that cardiac death will follow extubation in a timeframe consistent with organ procurement.

Consent

Consent for withdrawal of care and procurement of organs must be obtained from the legal next of kin (which may be a family member, designated health care representative or health care surrogate). Consent must also be obtained for any donation-related procedures prior to death (which typically includes heparin infusion to prolong organ viability[22] and the possibility of femoral catheters).

Clearance from the medical examiner must be obtained in applicable cases (including deaths due to accident, homicide, suicide…).

Procedure

Life sustaining measures are then discontinued (typically consisting of

extubation) usually in the operating room. Death is pronounced typically ≈ 2 minutes after cardiac activity becomes insufficient to generate a pulse, because limited data indicates that circulation will not spontaneously return[23] (NB: EKG activity does not need to cease). After declaration of death, cold perfusion of organs is performed and they are procured.

To avoid potential conflicts of interest, no member of the transplant team can participate in end-of-life care nor the declaration of death[19]. About 20% of the time, the progression to cardiac death does not occur in a timeframe that permits organ retrieval. In these cases, organ donation is cancelled, the family must be immediately notified, and end-of-life care continues.

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14. Cerebrospinal fluid

14.1. General information

Cerebrospinal fluid **(CSF)** surrounds the brain and spinal cord, and may function as a shock absorber for the CNS. It may also serve an immunological function analogous to the lymphatic system[1]. It circulates within the subarachnoid space, between the arachnoid and the pial membranes.

CSF is normally a clear colorless fluid with a specific gravity of 1.007 and a pH of ≈ 7.33-7.35.

Production

80% of CSF is produced by the choroid plexuses, located in both lateral ventricles (accounts for ≈ 95% of CSF produced in the choroid plexuses) and in the 4th ventricle. Most of the rest of intracranial production occurs in the interstitial space[2]. A small amount may also be produced by the ependymal lining of the ventricles. In the spine, it is produced primarily in the dura of the nerve root sleeves. *Table 14-1* shows properties of CSF production, volumes and pressures.

Table 14-1 Normal CSF production, volumes, and pressure

Property	—— Peds ——		Adult
	Newborn	1-10 yrs	
total volume (ml)	5		150 (50% intracranial, 50% spinal)
formation rate	25 ml/d		≈ 0.3-0.35 ml/min (≈ 450-750 ml/d)
pressure* (cm of fluid)	9-12	mean: 10 normal: < 15	adult: 7-15 (> 18 usually abnormal) young adult: < 18-20

* as measured in the lumbar subarachnoid space, with the patient relaxed in the lateral decubitus position

Production rate: In the adult, CSF is produced at a rate of about 0.3 ml/min (*see Table 14-1*). In terms that are clinically relevant, this approximates 450 ml/24hrs, which means that in an adult, the CSF is “turned over” ≈ 3 times every day. The rate of formation is *independent* of the intracranial pressure[3] (except in the

limiting case when ICP becomes so high that cerebral blood flow is reduced[4]).

Absorption

CSF is absorbed primarily by arachnoid villi (granulations) that extend into the dural venous sinuses. Other sites of absorption include the choroid plexuses and lymphatics. The rate of absorption is pressure dependent[5].

14.2. CSF constituents

The composition of CSF differs slightly in the ventricles where the majority of it is produced compared to the lumbar subarachnoid space.

CELLULAR COMPONENT

In normal adult CSF, there are 0-5 lymphocytes or mononuclear cells per mm^3, and no polys (PMNs) or RBCs. In the absence of RBCs, 5-10 WBCs per mm^3 is suspicious, and > 10 WBCs per mm^3 is definitely abnormal.

TRAUMATIC TAP

Differentiating true leukocytosis from traumatic tap

When many RBCs and WBCs are present in the CSF due to a traumatic tap **(TT)**, it may be important to tell if the WBCs are elevated or if they are present in the same ratio as in the peripheral blood. In non-anemic patients, there should be ≈ 1-2 WBCs for every 1000 RBCs (as a correction[6 (p 176)]: subtract 1 WBC for every 700 RBCs[6 (p 176)]). In the presence of anemia or peripheral leukocytosis, use **Fishman's formula**[6 (p 176)] shown in *Eq 14-1* to estimate the original WBC count in the CSF before the TT,

$$WBC_{CSF\ ORIGINAL} = WBC_{CSF} - \frac{WBC_{BLOOD} \times RBC_{CSF}}{RBC_{BLOOD}} \qquad \textbf{Eq 14-1}$$

where WBC_{CSF} ORIGINAL = WBC count in the CSF before the TT, WBC_{CSF} & RBC_{CSF} = WBC & RBC counts measured in the CSF, and WBCBLOOD & RBCBLOOD = WBC & RBC per mm^3 in the peripheral blood.

Estimating true total CSF protein content with a traumatic tap

If the hemogram and peripheral protein are normal, then have the cell count and protein content run on the same tube, and the correction is[6 (p 176)]:

• subtract 1 mg per 100 ml of protein for every 1000 RBC per mm^3

Differentiating SAH from traumatic tap

For typical findings in SAH, *see page 1038*. Some features helpful in differentiating SAH from TT are shown in *Table 14-2*.

Table 14-2 Features distinguishing traumatic tap from SAH

Feature	Traumatic tap (TT)	SAH
RBC count (and gross appearance of bloodiness)	declines as CSF drains (compare first tube to last tube)	usually > 100,000 RBCs/mm^3, changes little as CSF drains
ratio of WBC:RBC	similar to the ratio in peripheral blood (see *Differentiating true leukocytosis from traumatic tap* above)	usually promotes a leukocytosis (elevated WBC count)
supernatant	clear	xanthochromic* (rarely in < 2 hrs, present in 70% by 6 hrs, and > 90% by 12 hrs after SAH)
clotting of fluid	usually clots if erythrocyte count > 200,000/mm^3	usually does not clot
protein concentration	fresh bleeding elevates CSF protein from normal by only ≈ 1 mg per 1000 RBC	blood breakdown products elevate this more than TT (measured protein exceeds the sum of normal protein + 1 mg protein/1000 RBC)
repeat LP at higher level	usually clear	remains bloody
opening pressure	usually normal	usually elevated

* NB: other conditions can cause xanthochromia

CSF CONSTITUENTS

Table 14-3 CSF solutes [6 (p 169), 7]

(for CEA, AFP, & hCG, see *Tumor markers*, page 720)

Data from Table 6-1 of "Cerebrospinal Fluid in Diseases of the Nervous System" by Robert A. Fishman, M.D., © 1980, W. B. Saunders Co., Philadelphia, PA, used with permission

Constituent	Units	CSF	Plasma	CSF:plasma ratio
osmolarity	mOsm/L	295	295	1.0
H_2O content		99%	93%	
sodium	mEq/L	138	138	1.0
potassium	mEq/L	2.8	4.5	0.6
chloride	mEq/L	119	102	1.2
calcium	mEq/L	2.1	4.8	0.4
pCO_2	mm Hg	47	41*	1.1
pH		7.33	7.41	
pO_2	mm Hg	43	104*	0.4
glucose	mg/dl	60	90	0.67
lactate	mEq/L	1.6	1.0*	1.6
pyruvate	mEq/L	0.08	0.11*	0.73
lactate:pyruvate		26	17.6*	
total protein†	mg/dl	35	7000	0.005
albumin	mg/L	155	36600	0.004
IgG	mg/L	12.3	9870	0.001

* arterial plasma

† Note: CSF protein is lower in ventricular fluid than in lumbar subarachnoid space

Table 14-4 Variations with age

Age group	WBC /mm³	RBC /mm³	Protein (mg/dl)	Glucose (mg/dl)	Glucose ratio (CSF:plasma)
newborn					
preemie	10	many	150	20-65	0.5-1.6
term	7-8	mod	80	30-120	0.4-2.5
infants					
1-12 mos	5-6	0	15-80		
1-2 yrs	2-3	0	15		
young child	2-3	0	20		
child 5-15 yrs	2-3	0	25		
adolescent & adult	3	0	30	40-80	0.5
senile	5	0	40*		

* normal CSF protein rises ≈ 1 mg/dl per year of age in the adult

Table 14-5 CSF findings in various pathologic conditions (adult values)*

Condition	OP (cm H_2O)	Appearance	Cells (per mm^3)	Protein (mg%)	Glucose (% serum)	Miscellaneous
normal	7-18	clear colorless	0 PMN, 0 RBC 0-5 monos	15-45	50	
acute purulent meningitis	freq ↑	turbid	few-20K (WBCs mostly PMNs)	100-1000	< 20	few cells early or if treated
viral meningitis & encephalitis	nl	nl	few-350 WBCs (mostly monos)	40-100	nl	PMNs early
Guillain-Barré	nl	nl	nl	50-1000	nl	protein ↑, freq. IgG
polio	nl	nl	50-250 (monos)	40-100	nl	
TB meningitis†	freq ↑	opalescent, yellow, fibrin clot on standing	50-500 (lymphocytes and monocytes)	60-700	20-40	PMN early, (+) AFB culture, (+) Ziel-Neelson stain
fungal meningitis	freq ↑	opalescent	30-300 (monos)	100-700	< 30	(+) India ink prep with cryptococcus
amebic meningoencephalitis (*Naegleria*)	freq ↑	cloudy, may be hemorrhagic	↑ WBCs (400-26K), ↑ RBCs	↑	nl or ↓	negative Gram stain; wet mount → motile trophozoites (*see page 375*)
parameningeal infection	↑ if block	nl	WBCs nl or ↑ (0-800)	↑	nl	e.g. spinal epidural abscess
traumatic‡ (bloody) tap	nl	bloody; supernatant colorless	RBC:WBC ratio ≈ as in peripheral	slight ↑	nl	RBCs ↓ in successive tubes; no xanthochromia
SAH‡	↑	bloody; supernatant xanthochromic	early: ↑ RBCs	50-400	nl or ↓	RBCs disappear in 2 wks, xanthochromia may persist for weeks
			late: ↑ WBCs	100-800		
multiple sclerosis (MS)§	nl	nl	5-50 monos	nl-800	nl	usually ↑ gamma globulins (oligoclonal)

* abbreviations: OP = opening pressure; nl = normal; ↑ = increased; ↓ = decreased; freq = frequently

† the CSF findings in TB meningitis are almost pathognomonic when they occur in combination; 20-30% have acid-fast bacilli in their CSF sediment smears

‡ to differentiate traumatic tap from SAH, also see *Differentiating SAH from traumatic tap*, page 298

§ for more information on the CSF in MS, *see page 64*

14.3. Artificial CSF

A number of formulations of "artificial" CSF have been proposed over the years in order to more closely mimic the pH, osmolarity, CO_2, and membrane active ion concentration of CSF. In many instances, normal saline **(NS)** has been used in brain surgery, probably without consequence. However, renewed interest in the subject of artificial CSF has been brought about by the use of neuroendoscopy, with possible reactions to nonphysiologic solutions when large volumes of fluid are exchanged, as occurs during some of these procedures. An

actual reaction to NS, however, has never been proven.

In addition to simulating the constituents of CSF, it may also be well to insure a physiologic temperature of the solution[8].

Elliott's solution

AKA Solution B of Elliott and Jasper[9, 10]: an elaborate formulation that was widely used in the past.

14.4. CSF fistula (cranial)

Key concepts:

> • suspect in posttraumatic otorrhea/rhinorrhea or recurrent meningitis
> • management strategy: 1) confirm the fluid is CSF, 2) identify the site of origin of the leak, 3) determine etiology/mechanism
> • most bedside tests are unreliable and include: "reservoir sign", target/halo sign, qualitative glucose
> • most accurate confirmatory test is $ß_2$-transferrin
> • CT cisternography is the test of choice for localizing site of fistula

AKA CSF leak. Two major subgroups (omitting the ambiguous category of "spontaneous")[11]:

1. traumatic (or posttraumatic): may occur acutely or may be delayed
   A. post-procedure (iatrogenic). Including: post-transsphenoidal surgery and post skull base surgery
   B. posttraumatic (more common): 67-77% of cases
2. nontraumatic
   A. high pressure
      1. hydrocephalus
      2. tumor
   B. normal pressure
      1. congenital defects
      2. bony erosion from infection or necrosis
      3. focal atrophy (olfactory or sellar)

CSF fistula should be suspected in patients with otorrhea or rhinorrhea after

head trauma, or in patients with recurrent meningitis.

Possible routes of egress of CSF

1. mastoid air cells (especially after p-fossa surgery, e.g. for vestibular schwannoma **(VS)**, *see page 630*)
2. sphenoid air cells (especially post-transsphenoidal surgery)
3. cribriform plate/ethmoidal roof (floor of frontal fossa)
4. frontal air cells
5. herniation into empty sella and then into sphenoid air sinus
6. along path of internal carotid artery
7. Rosenmüller's fossa: located just inferior to cavernous sinus, may be exposed by drilling off anterior clinoids to allow access to ophthalmic artery aneurysms
8. site of the opening of the transient lateral craniopharyngeal canal
9. percutaneously through a surgical or traumatic wound
10. petrous ridge or internal auditory canal: following temporal bone fracture or vestibular schwannoma surgery (*see page 630*). Then either:
    A. **rhinorrhea**: through middle ear → eustachian tube → nasopharynx
    B. **otorrhea**: via perforated tympanic membrane → external auditory canal

TRAUMATIC FISTULA

Occur in 2-3% of all patients with head injury, 60% occur within days of trauma, 95% within 3 months[12]. 70% of cases of CSF rhinorrhea stop within 1 wk, and usually within 6 mos in the rest. Non-traumatic cases cease spontaneously in only 33%. Adult:child ratio is 10:1, rare before age 2 yrs. In children the incidence of CSF leaks is less than 1% of closed head injuries[13]. Anosmia is common in traumatic leaks (78%), rare in spontaneous[14]. Most (80-85%) CSF otorrhea ceases in 5-10 days.

CSF fistula occurred in 8.9% of 101 cases of penetrating trauma, and increases the infection rate over those penetrating injuries without fistula (50% vs. 4.6%)[15]. It is reported to occur post-op in up to 30% of cases of skull-base surgery[16].

NONTRAUMATIC CSF FISTULA

Nontraumatic leaks primarily occur in adults > 30 yrs. Often insidious. May

be mistaken for allergic rhinitis. Unlike traumatic leaks, these tend to be intermittent, the sense of smell is usually preserved, and pneumocephalus is uncommon[17].

Sometimes associated with the following[18]

1. agenesis of the floor of the anterior fossa (cribriform plate) or middle fossa
2. empty sella syndrome: primary or post transsphenoidal surgery (*see page 660*)
3. increased ICP and/or hydrocephalus
4. infection of the paranasal sinuses
5. tumor: including pituitary adenomas (*see page 634*), meningiomas
6. a persistent remnant of the craniopharyngeal canal[19]
7. AVM[17]
8. congenital anomalies: most involve dehiscence of bone
    A. dehiscence of the footplate of the stapes (a congenital abnormality) which can produce CSF rhinorrhea via the eustachian tube[17]
    B. dehiscence below foramen rotundum

Posterior fossa

1. pediatric: usually presents with either meningitis or hearing loss
    A. preserved labyrinthine function (hearing and balance): these usually present with meningitis. 3 usual routes of fistula:
        1. facial canal: can fistulize into middle ear
        2. petromastoid canal: along path of arterial supply to mucosa of mastoid air sinuses
        3. Hyrtl’s fissure (AKA tympanomeningeal fissure): links p-fossa to hypotympanum
    B. anomalies of labyrinth (hearing lost): one of several types of Mundini dysplasias, usually presenting with rounded labyrinth/cochlea that permits CSF to erode through oval or round window into auditory canal
2. adult: usually presents with conductive hearing loss with serous effusion, meningitis (often following an episode of otitis media), or cerebral abscess. Occurs most commonly through middle fossa. May be due to arachnoid granulations eroding into air sinus compartment

Spinal

Often presents with postural headache associated with neck stiffness and tenderness[20] (*see page 305*).

MENINGITIS IN CSF FISTULA

Incidence with posttraumatic CSF leak: 5-10%, increases as leak persists > 7 days. Meningitis is more common with spontaneous fistula. Risk may be higher in post-neurosurgical CSF fistula than in post-traumatic due to elevated ICP common in latter (forces CSF outward). If site of leak unidentified prior to attempted surgical treatment, 30% develop a recurrent leak post-op, with 5-15% of these developing meningitis before leak is stopped[21].

Meningitis may promote inflammatory changes at the site of the leak, with a resultant cessation of the leak.

Pneumococcal meningitis is the most common pathogen (83% of cases[22]), mortality is lower than in pneumococcal meningitis without underlying fistula (< 10% vs. 50%), possibly because the latter is frequently seen in elderly debilitated patients. Prognosis in children is worse[12].

EVALUATION

Determining if rhinorrhea or otorrhea is due to a CSF fistula

1. characteristics of the fluid suggesting the presence of CSF
   A. fluid is as clear as water (unless infected or admixed with blood)
   B. fluid does not cause excoriation within or outside the nose
   C. patients with rhinorrhea describe the taste as salty
2. confirmatory tests
   A. **β_2-transferrin**: present in CSF, but absent in tears, saliva, nasal exudates and serum (except for newborns and patients with liver disease)[23, 24]. The only other source is the vitreous fluid of the eye. detected by protein electrophoresis. ≈ 0.5 ml needs to be placed in a sterile container, packed in dry ice, and shipped to a lab that can perform this study. Very sensitive & specific
   B. collect fluid and obtain quantitative **glucose** (urine glucose detection strips may be positive even with excess mucus). Test the fluid shortly after collection to minimize fermentation. Normal CSF glucose is > 30

mg% (usually lower with meningitis) whereas lacrimal secretions and mucus are usually < 5 mg%. A negative test is more helpful since it rules out CSF (except in hypoglycorrhachia), but there is a 45-75% chance of false positive[25 (p 1638)]

C. "**ring sign**": when a CSF leak is suspected but the fluid is blood tinged, allow the fluid to drip onto linen (sheet or pillowcase). A ring of blood with a larger concentric ring of clear fluid (so called "double ring" or halo sign) suggests the presence of CSF. An old, but unreliable, sign

D. **reservoir sign**: a gush of fluid that occurs with a certain head position. Most commonly when first sitting up after a period of recumbency. Thought to indicate drainage of CSF pooled in the sphenoid sinus. Not reliable[26]

3. radiographic signs: pneumocephalus on CT or skull x-ray. Pneumocephalus occurs in ≈ 20% of patients with CSF leaks[27 (p 280)]
4. cisternogram: intrathecal injection of radionuclide tracer followed by scintigram or injection of radioopaque contrast followed by CT scan (*see below*)
5. anosmia is present in ≈ 5% of CSF leaks
6. following skull-base surgery (especially involving greater superficial petrosal nerve) there may be a **pseudo-CSF rhinorrhea** possibly due to nasal hypersecretion from imbalanced autonomic regulation of the nasal mucosa[16] ipsilateral to the surgery. Often accompanied by nasal stuffiness and absent ipsilateral lacrimation, and occasionally by facial flushing

To localize site of CSF fistula

90% of the time, localization does not require water-soluble contrast CT cisternography **(WS-CTC)** (*see below*).

1. CT: to detect pneumocephalus, fractures, skull base defects, hydrocephalus and obstructive neoplasms. Include thin <u>coronal</u> cuts or reconstructions through anterior fossa all the way back to the sella turcica
   A. non-contrast (optional): to demonstrate bony anatomy
   B. with IV contrast: leak site is usually associated with abnormal enhancement of adjacent brain parenchyma (possibly from inflammation)
2. water-soluble contrast CT cisternography (procedure of choice): *see below*
3. plain skull x-ray (helpful in only 21%)

4. MRI: may provide additional information for localization and can R/O p-fossa mass, tumor, and empty sella better than CT. Both CT and MRI can R/O hydrocephalus. T2WI fast spin-echo sequences with fat suppression and video image reversal have been used to visualize CSF flow (sensitivity and specificity are 0.87 and 0.57 respectively)[28]
5. older tests (abandoned in favor of above):
   A. **radionuclide cisternography (RNC)**: may be useful in leaks too slow or small to show up on WS-CTC. Various radioactive agents have been used, including: radioiodinated human serum albumin (RIHSA)[17, 29], and 500 µCi Indium^{111} DPTA. Cotton pledgets are packed intranasally (anterior nasal roof, posterior nasal roof, sphenoethmoidal recess, middle meatus, and posterior floor of the nose) and are marked so that their location is known. Radiotracer is then injected intrathecally usually by lumbar puncture. Scans are performed in lateral, AP and posterior view. A protocol using In^{111} DTPA is to obtain a scan shortly after injection. At 4 hours post-injection, the scan is repeated, and 0.5 ml of blood is drawn (to measure serum activity), and the pledgets are removed. The pledgets are then individually placed in a well-counter and a ratio is calculated for pledget radioactivity relative to serum. A ratio ≤ 1.3 is normal, and a ratio > 1.3 suggests leak. If no leak, the nose can be repacked and the study repeated the following morning.
      Leaks into frontal sinus will empty into nasopharynx anterior to the middle concha, unlike leaks through cribriform plate. RNC identifies the site in only 50%. May be misleading[14] with possible contamination after several hours from absorption of radioisotope into the bloodstream and accumulation in the mucosal glands of the turbinates. Patient positioning may also contaminate other pledgets
   B. intrathecal (visible) dye studies: some success with indigo carmine or fluorescein (*see page 144*) with little or no complications (✖ methylene blue is neurotoxic and should not be used, *see page 144*)

Water-soluble contrast CT cisternography

Procedure of choice. This test is performed if:

1. no site identified on plain CT (with coronals)
2. when patient is leaking clinically (the site is only sometimes identified in the absence of an active leak)
3. when multiple bony defects are identified, and it is essential to determine

which site is actively leaking

4. if a bony defect seen on plain CT does not have associated changes of abnormal enhancement of adjacent brain parenchyma

Technique[30]

Use iohexol (*see* *page 122*) 6-7 ml of 190-220 mg/ml) injected into lumbar subarachnoid space via 22 gauge spinal needle (or 5 ml via C1-2 puncture). Patient positioned in -70° Trendelenburg **x** 3 min prone with neck gently flexed, in CT they are kept prone with head hyperextended with 5 mm coronal cuts with 3 mm overlap (use 1.5 mm cuts if necessary). May need provocative maneuvers (coronal scans prone (brow up) or in position of leak, intrathecal saline infusion (requires Harvard pump)[21]…).

Look for accumulation of contrast in air sinuses. Apparent discontinuity of bone on CT without extravasation of contrast is probably not the site of leakage (bone discontinuities may be mimicked by partial volume averaging on CT).

TREATMENT

Acutely after trauma, observation is justified as most cases cease spontaneously.
Prophylactic antibiotics: Controversial. There was no difference in the incidence or morbidity of meningitis between treated and untreated patients[31]. Furthermore, the risk of selecting resistant strains appears real[12] and is therefore usually avoided.

FOR PERSISTENT POSTTRAUMATIC OR POST-OP LEAKS

Non-surgical treatment

1. measures to lower ICP:
   A. bed rest: although recumbency may ameliorate symptoms, there is no other benefit from bed rest[32]
   B. avoid straining (stool softeners) and avoid blowing nose
   C. acetazolamide (250 mg PO QID) to reduce CSF production
   D. modest fluid restriction (caution post-transsphenoidal because of possible DI (*see* *page 15*): 1500 ml/day in adults, 75% of maintenance/day in peds
2. if leak persists (caution: first R/O obstructive hydrocephalus with CT or MRI)

A. **LP**: q d to BID (lower pressure to near atmospheric or until H/A)
OR
B. continuous **lumbar drainage (CLD)**: via percutaneous catheter. Two (of many) management options:
   1. keep HOB elevated 10-15° and place drip chamber at shoulder level (lower the chamber if leak persists)
   2. allow 15-20 cc to drain, then clamp tubing. Repeat q 1 hour

- CLD may require ICU monitoring. If patient deteriorates with drain in place: immediately stop drainage, place patient flat in bed (or slight Trendelenburg), start 100% O_2, get CT or bedside cross-table skull x-ray (to R/O tension pneumocephalus due to drawing in of air)

3. surgical treatment in persistent cases (*see below*)

SURGICAL TREATMENT

Indications for surgical intervention

1. traumatic CSF leak that persists > 2 weeks in spite of non-surgical measures
2. spontaneous leaks and those of delayed onset following trauma or surgery: usually require surgery because of a high incidence of recurrence
3. leaks complicated by meningitis

Petrous bone

May present as otorrhea or as rhinorrhea (via the eustachian tube).

1. following posterior fossa surgery: *see page 630* for treatment following vestibular schwannoma surgery
2. following mastoid fractures: may be approached via extensive mastoidectomy[17]
3. due to dehiscence of the footplate of the stapes: may require obliteration of the middle ear and eustachian tube through a tympanomeatal flap[17]

Leaks through cribriform plate/ethmoidal roof

Extradural approach: Generally preferred by ENT surgeons[33]. If a frontal craniotomy is being performed, an intradural approach should be used since problems may arise in dissecting the dura off of the floor of the frontal fossa,

wherein the dura almost always tears and then it is difficult to know if an identified tear is the cause of the leak or if it is iatrogenic. Fluorescein dye mixed with CSF injected intrathecally may help demonstrate the leak intraoperatively (CAUTION: must be diluted to reduce risk of seizures, *see page 144*).

Intradural approach: Generally the procedure of choice[34]. If the fistula site is unidentified preoperatively, use a bifrontal bone flap.

General techniques of intradural approach:

Close bone defects with fat, muscle, cartilage, or bone.

Close dural defect with fascia lata, temporalis muscle fascia, or pericranium. Fibrin glue may be used to help hold tissue in place.

If the leak is unidentified pre-op and intra-op, then pack both cribriform plates and sphenoid sinus (incise dura over tuberculum sellae, drill through bone to reach sphenoid sinus, remove mucosa or pack it inferiorly, pack with fat).

Post op: lumbar drain after craniotomy is controversial. Some feel CSF pressure may help enhance the seal[35]. If used, place the drip chamber at the level of shoulder for 3-5 days (for precautions, *see above*).

Consider shunt (LP or VP) if elevated ICP or hydrocephalus is demonstrated.

Leaks into sphenoid sinus (including post-transsphenoidal surgery leak)

1. LP BID or CLD: as long as pressure > 150 mm H_2O or CSF xanthochromic
   A. if leak persists > 3 days: repack sphenoid sinus and pterygoid recesses with fat, muscle, cartilage and/or fascia lata (must reconstruct floor of sella, packing alone is inadequate). Some recommend against muscle since it putrefies and shrinks. Continue LP or CLD as above for 3-5 days post-op
   B. if leak persists > 5 days: lumboperitoneal shunt (first R/O obstructive hydrocephalus)
2. more difficult surgical approach: intracranial (intradural) approach to medial aspect of middle cranial fossa
3. consider transnasal sellar injection of fibrin glue under local anesthesia[36]

14.5. Intracranial hypotension

May be spontaneous (*see below*), post-traumatic (including iatrogenic, e.g. post-LP).

SPONTANEOUS INTRACRANIAL HYPOTENSION (SIH)

The syndrome of spontaneous intracranial hypotension is characterized by the following in the absence of antecedent trauma or LP (or epidural injection…)[37]:

1. orthostatic headache: dramatically worse when upright, improved in recumbency
2. low CSF pressure
3. diffuse pachymeningeal enhancement (cerebral and/or spinal) on MRI

In most cases, the underlying etiology is thought to be a spontaneous CSF leak from a spinal meningeal diverticulum or dural tear[20].

Clinical features

Most patients have orthostatic headache. Onset is often sudden, and may be associated with spinal pain in a specific location. Atypical patients have been described without H/A, or H/A that is non-positional, without pachymeningeal enhancement on MRI[38], with clinical signs of encephalopathy, cervical myelopathy, or parkinsonism[39]. Since some patients may have normal intracranial pressure, the term "CSF hypovolemia" has been suggested[40].

Evaluation

1. brain MRI. Findings:
   A. ★ diffuse pachymeningeal enhancement (cerebral and/or spinal) is common
   B. brain descent with low lying cerebellar tonsils occurred in 36%[39]
   C. reversible pituitary enlargement with a convex superior margin[41]
   D. subdural hematomas (in 20%) and nonhemorrhagic subdural fluid collections (in 23%) in one series of 40 patients with SIH[42]
   E. small ventricles and cisterns may be seen
2. spinal MRI: may show evidence of CSF leak. If there is focal spine pain, the leak will often be near this location
3. radioisotope cisternography: abnormal in 90%. Revealed the site of CSF leak in 40%[39].

Treatment

Treatment includes:

1. bed rest
2. analgesics
3. hydration
4. caffeine
5. epidural blood patch **(EBP)** for appropriate cases: *see page 59*

Subdural fluid collections occasionally require intervention (usually drainage of the subdural and blood patching of the spinal leak, if identified).

Outcome

Complete resolution of H/A was achieved in 70% (usually in days to weeks), and was higher in patients receiving EBP, and was lower with multiple sites of CSF leak[39].

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15. Hydrocephalus

[EPIDEMIOLOGY

Estimated prevalence: 1-1.5%.

Incidence of congenital hydrocephalus is ≈ 0.9-1.8/1000 births (reported range from 0.2 to 3.5/1000 births[1]).

FUNCTIONAL CLASSIFICATION

Two main functional subdivisions of hydrocephalus (HCP)

1. **obstructive** (AKA non-communicating): block proximal to the arachnoid granulations **(AG)**. On CT or MRI: enlargement of ventricles proximal to block (e.g. obstruction of aqueduct of Sylvius → lateral and 3rd ventricular enlargement out of proportion to the 4th ventricle, sometimes referred to as triventricular hydrocephalus)
2. **communicating** (AKA non-obstructive): CSF circulation blocked at level of AG

SPECIAL FORMS OF HYDROCEPHALUS AND "PSEUDOHYDROCEPHALUS"

1. conditions that are not actually hydrocephalus "pseudohydrocephalus"
   A. **hydrocephalus ex vacuo**: enlargement of the ventricles due to loss of cerebral tissue (cerebral atrophy), usually as a function of normal aging, but accelerated or accentuated by certain disease processes (e.g. Alzheimer's disease, Creutzfeldt-Jakob disease, traumatic brain injury). For means of differentiating from true hydrocephalus, *see page 906*
   B. otitic hydrocephalus: obsolete term used to describe the increased intracranial pressure seen in patients with otitis media (see see *Idiopathic intracranial hypertension (IIH)*, page 713)
   C. external hydrocephalus: seen in infancy, enlarged subarachnoid space with increasing OFCs and normal or mildly dilated ventricles *see page*

307

D. hydranencephaly: a post-neurulation defect (*see page 243*). Total or near-total absence of the cerebrum most commonly due to bilateral ICA infarcts. It is critical to differentiate this from severe ("maximal") hydrocephalus **(HCP)** since shunting for true HCP may produce some re-expansion of the cortical mantle (*see page 244* for means to differentiate)

2. normal pressure hydrocephalus **(NPH)**: *see page 329*
3. entrapped fourth ventricle: *see page 309*
4. arrested hydrocephalus: *see page 309*

External hydrocephalus (AKA benign external hydrocephalus)

Key concepts:

> • enlarged subarachnoid spaces over the frontal poles in the first year of life
> • ventricles are normal or minimally enlarged
> • may be distinguished from subdural hematoma by the "cortical vein sign"
> • usually resolves spontaneously by 2 years of age

Enlarged subarachnoid space (usually over the cortical sulci of the frontal poles) seen in infancy (primarily in the first year of life) usually accompanied by abnormally increasing head circumference with normal or mildly dilated ventricles[2]. There are often enlarged basal cisterns and widening of the anterior interhemispheric fissure. No other symptoms or signs should be present (although there may be slight delay only in motor milestones due to the large head). Etiology is unclear, but a defect in CSF resorption is postulated. External hydrocephalus **(EH)** may be a variant of communicating hydrocephalus[3]. No predisposing factor may be found in some cases, although EH may be associated with some craniosynostoses[4] (especially plagiocephaly) or it may follow intraventricular hemorrhage or superior vena cava obstruction.

Differential diagnosis: EH is probably distinct from benign subdural collections (or extra-axial fluid) of infancy (*see page 904*). ★ EH must be distinguished from symptomatic chronic extra-axial fluid collections (or chronic subdural hematoma), which may be accompanied by seizures, vomiting, headache… (*see page 905*) and may be the result of child abuse. With EH, MRI or CT may demonstrate cortical veins extending from the surface of the brain to the inner table of the skull coursing through the fluid collection ("**cortical vein sign**"), whereas the collections in subdural hematomas compress the subarachnoid space

which apposes the veins to the surface to the brain[5, 6].

Treatment: EH usually compensates by 12-18 mos age without shunting[7]. Recommend: follow serial ultrasound and/or CT to rule out abnormal ventricular enlargement. Emphasize to parents that this does not represent cortical atrophy. Due to increased risk for positional molding, parents may need to periodically reposition the head while the child is sleeping[8].

A shunt may rarely be indicated when the collections are bloody (consider the possibility of child abuse) or for cosmetic reasons for severe macrocrania or frontal bossing.

X-LINKED HYDROCEPHALUS

Inherited hydrocephalus **(HCP)** with phenotypic expression in males passed on through carrier mothers who are phenotypically normal. Classical phenotypic expression will skip single generations.

Incidence: 1/25,000 to 1/60,000. Prevalence: ≈ 2 cases per 100 cases of hydrocephalus.

Gene located on Xq28[151-153].

Pathophysiology

L1CAM membrane bound receptor plays a significant role in CNS development for axonal migration to appropriate target locations through Integrin cell adhesion molecules and MAP Kinase signal cascade[151-153].

Abnormal gene expression results in poor differentiation and maturation of cortical neurons macroscopic anatomical abnormalities (bilateral absence of pyramidal tracts, see below)

Cytoplasmic domain loss of function mutations result in severe L1 syndrome, whereas mutations retaining expression of some functional protein (component imbedded in cell membrane) leads to mild L1 syndrome.

L1 syndromes

Classical syndromes include CRASH (corpus callosum hypoplasia, retardation, adducted thumbs (clasp thumbs), spastic paralysis, HCP), MSAS (mental handicap, aphasia, shuffling gate, adducted thumbs), HSAS (HCP with stenosis of the aqueduct of sylvius). Spectrum of disease also includes x-linked agenesis of the corpus callosum **(ACC)**, and spastic paraparesis type 1[151, 152].

Recent delineations[153]:

- mild L1 syndrome: adducted thumbs, spastic paralysis, hypoplasia of CC
- severe L1 syndrome: as in mild L1 syndrome plus anterior cerebellar vermis hypoplasia, large massa intermedia, enlarged quadrigeminal plate, rippled ventricular wall following VP shunt placement (pathognomonic for X-linked HCP). Profound mental retardation in virtually all cases

Radiographic findings likely present if severe L1152:

1. severe symmetric HCP with predominant posterior horn dilation
2. hypoplastic CC/ACC
3. hypoplastic anterior cerebellar vermis
4. large massa intermedia
5. large quadrigeminal plate
6. rippled ventricular wall following VP shunt placement (pathognomonic)

Treatment: no intervention demonstrates improvement in retardation status in observational papers.

1. VP shunt: main purpose is management of head size for improved care by care-giver. Does not improve neurologic outcome
2. there are no current genetic therapies for L1CAM protein abnormalities
3. prenatal U/S: early (≈ 20-24 weeks gestational age) with frequent repeat scan in known carrier mothers. May allow for medically indicated termination early on
4. male infants with HCP and ≥ 2 clinical/radiographic signs should undergo genetic testing for L1CAM mutation detection for future pregnancy counseling[151]

"Arrested hydrocephalus"

The exact definition of this term is not generally agreed upon, and some use the term **compensated hydrocephalus** interchangeably. Most clinicians use these terms to refer to a situation where there is no progression or deleterious sequelae due to hydrocephalus that would require the presence of a CSF shunt. Patients and families should be advised to seek medical attention if they develop symptoms of intracranial hypertension (decompensation): headaches, vomiting, ataxia or visual symptoms[8].

Arrested hydrocephalus satisfies the following criteria in the absence of a CSF shunt:

1. near normal ventricular size
2. normal head growth curve

3. continued psychomotor development

Shunt independence

The concept of becoming independent of a shunt is not universally accepted[9]. Some feel that shunt independence occurs more commonly when the HCP is due to a block at the level of the arachnoid granulations (communicating hydrocephalus)[10], but others have shown that it can occur regardless of the etiology[11]. These patients must be followed closely as there are reports of death as late as 5 years after apparent shunt independence, sometimes without warning[10].

When to remove a disconnected or non-functioning shunt?

Note: a disconnected shunt may continue to function by CSF flow through an endothelialized subcutaneous tract. Recommendations on whether or not to repair vs. remove a disconnected or non-functioning shunt:

1. when in doubt, shunt
2. indications for shunt repair (vs. removal)
   A. marginally functioning shunts
   B. the presence of any signs or symptoms of increased ICP (vomiting, upgaze palsy, sometimes H/A alone[12]…)
   C. changes in cognitive function, ↓ attention span, or emotional changes
   D. patients with aqueductal stenosis or spina bifida: most are shunt dependent
3. because of risks associated with shunt removal, surgery for this purpose alone should be performed only in the situation of a shunt infection[13]
4. patients with a nonfunctioning shunt should be followed closely with serial CTs, and possibly with serial neuropsychological evaluations

Entrapped fourth ventricle

AKA isolated fourth ventricle: 4th ventricle that neither communicates with the 3rd ventricle (through sylvian aqueduct) nor with the basal cisterns (through foramina of Luschka or Magendie). Usually seen with chronic shunting of the lateral ventricles, especially with post-infectious hydrocephalus (fungal, in particular) or in those with repeated shunt infections. Possibly as a result of

adhesions forming from prolonged apposition of the ependymal lining of the aqueduct due to the diversion of CSF through the shunt. Occurs in 2-3% of shunted patients[14]. May also occur in Dandy Walker malformation (*see page 240*) if the aqueduct is also obstructed. The choroid plexus of the 4th ventricle continues to produce CSF which enlarges the ventricle when there is 4th ventricular outlet obstruction or obstruction at the level of the arachnoid granulations.

Presentation may include:

1. headache
2. lower cranial nerve palsies: swallowing difficulties
3. pressure on the floor of the 4th ventricle may compress the facial colliculus (*see page 844*) → facial diplegia and bilateral abducens palsy
4. ataxia
5. reduced level of consciousness
6. nausea/vomiting
7. may also be an incidental finding (NB: some “atypical” findings, such as reduced attention span, may be related)

Treatment

Treatment of the entrapped 4th ventricle may alleviate associated slit ventricles[15]. Most surgeons advocate shunting the ventricle either with a separate VP shunt, or linking into an existing shunt. Options:

1. usual first choice: insertion from below the tonsils under direct vision. The catheter may be brought out at the dural suture line, and may be anchored here by use of an angle adapter sutured to the dura
2. passage through a cerebellar hemisphere: potential complications include delayed injury to the brainstem by the catheter tip as the brainstem moves into its normal position with drainage of the 4th ventricle. This may be avoided by bringing the catheter into the 4th ventricle at a slight angle through the cerebellar hemisphere
3. Torkildsen shunt (ventriculocisternal shunt) is an option for obstructive hydrocephalus if it is certain that the arachnoid granulations are functional (usually not the case with hydrocephalus of infantile onset)
4. an LP shunt may be considered when the 4th ventricle outlets are patent

Cranial nerve palsies may occur with shunting of the 4th ventricle usually as a result of penetration of the brainstem by the catheter either at the time of

catheter insertion, or in a delayed fashion as the 4th ventricle decreases in size[16], but also possibly as a result of overshunting causing traction on the lower cranial nerves as the brainstem shifts posteriorly[14].

CT/MRI CRITERIA OF HYDROCEPHALUS

Numerous methods have been devised to attempt to quantitatively define hydrocephalus **(HCP)** (most date back to the early CT experience). Some are presented here for completeness. For radiologic features of *chronic* HCP, *see page 312*.

Hydrocephalus (HCP)

HCP is suggested when either[17]:

A. the size of both temporal horns **(TH)** is ≥ 2 mm in width (*see Figure 15-1*) (in the absence of HCP, the temporal horns should be barely visible), and the sylvian & interhemispheric fissures and cerebral sulci are not visible

OR

B. both TH are ≥ 2 mm, <u>and</u> the ratio $\frac{FH}{ID} > 0.5$ (where **FH** is the largest width of the frontal horns, and ID is the internal diameter from inner-table to inner-table at this level) (*see Figure 15-1*)

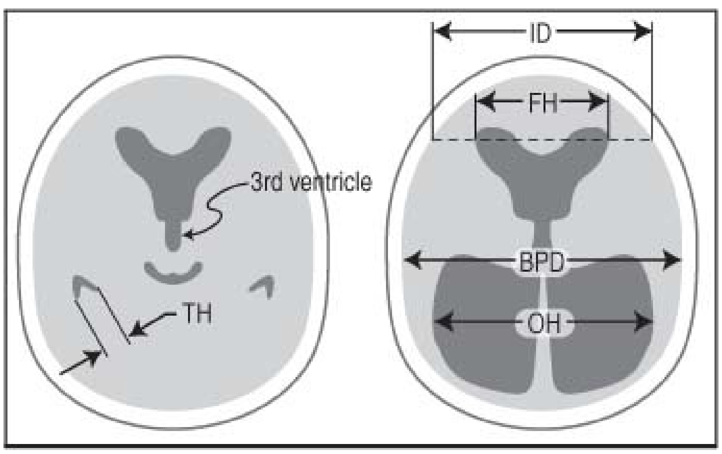


Figure 15-1 Linear ventricular measurement for CT, MRI or U/S Abbreviations: TH = temporal horns, FH = frontal horns, ID = internal diameter, BPD = biparietal diameter, OH = occipital horns

Other features suggestive of hydrocephalus (*see Figure 15-1* for measurements):

1. ballooning of frontal horns of lateral ventricles (“Mickey Mouse” ventricles) and/or 3rd ventricle (the 3rd ventricle should normally be slit-like)

2. periventricular low density on CT, or periventricular high intensity signal on T2WI on MRI suggesting **transependymal absorption**[A] of CSF
3. used alone, the ratio $\frac{FH}{ID} \begin{cases} < 40\% & \text{normal} \\ 40\text{-}50\% & \text{borderline} \\ > 50\% & \text{suggests hydrocephalus} \end{cases}$
4. **Evans ratio** 18 (or index)[B]: ratio of FH to <u>maximal</u> biparietal diameter **(BPD)** measured in the same CT slice: > 0.3 suggests hydrocephalus
5. sagittal MRI may show thinning and/or upward bowing of the corpus callosum

---

A. a misnomer: CSF does not actually penetrate the ependymal lining (proven with CSF labeling studies), probably represents stasis of fluid in brain adjacent to ventricles

B. NB: measurements that rely on the frontal horn diameter tend to underestimate hydrocephalus in pediatrics possibly because of disproportionate dilatation of the occipital horns in peds[19]

ETIOLOGIES OF HYDROCEPHALUS

HCP is either due to subnormal CSF reabsorption, or rarely to CSF overproduction (as with some choroid plexus papillomas; even here, reabsorption is probably defective in some as normal individuals could probably tolerate the slightly elevated CSF production rate of these tumors). The etiologies in one series of pediatric patients is shown in *Table 15-1*.

- congenital
  A. Chiari Type 2 malformation and/or myelomeningocele **(MM)** (usually occur together)
  B. Chiari Type 1 malformation: HCP may occur with 4th ventricle outlet obstruction
  C. primary aqueductal stenosis (usually presents in infancy, rarely in adult-hood)
  D. secondary aqueductal gliosis: due to intrauterine infection or germinal matrix hemorrhage[21]
  E. **Dandy Walker malformation**: atresia of foramina of Luschka & Magendie (*see page 240*). The incidence of this in patients with HCP is 2.4%
  F. X-linked inherited disorder: rare
- acquired

A. infectious (the most common cause of communicating HCP)
   1. post-meningitis (especially purulent and basal, including TB, cryptococcus (*see page 374*))
   2. cysticercosis
B. post-hemorrhagic (2nd most common cause of communicating HCP)
   1. post-SAH (*see page 1037*)
   2. post-intraventricular hemorrhage **(IVH)**: many will develop transient HCP. 20-50% of patients with large IVH develop permanent HCP
C. secondary to masses
   1. non neoplastic: e.g. vascular malformation
   2. neoplastic: most produce obstructive HCP by blocking CSF pathways, especially tumors around aqueduct, e.g. medulloblastoma. A colloid cyst can block CSF flow at the foramen of Monro. Pituitary tumor: suprasellar extension of tumor or expansion from pituitary apoplexy
D. post-op: 20% of pediatric patients develop permanent hydrocephalus (requiring shunt) following p-fossa tumor removal. May be delayed up to 1 yr
E. neurosarcoidosis: *see page 71*
F. "constitutional ventriculomegaly": asymptomatic. Needs no treatment
G. associated with spinal tumors[22]

Table 15-1 Etiologies of HCP in 170 pediatric patients with HCP[20]

congenital (without myelomeningocele)	38%
congenital (with MM)	29%
perinatal hemorrhage	11%
trauma/subarachnoid hemorrhage	4.7%
tumor	11%
previous infection	7.6%

DIFFERENTIAL DIAGNOSIS OF HYDROCEPHALUS

For etiologies of HCP, *see above*. Conditions that may mimic HCP but are not due to inadequate CSF absorption include:

1. atrophy: sometimes referred to as "hydrocephalus ex vacuo". Does not represent altered CSF hydrodynamics, but is rather loss of brain tissue (*see*

page 307)
2. hydranencephaly: *see page 243*
3. developmental anomalies where the ventricles appear enlarged:
   A. agenesis of the corpus callosum: *see page 246* (may occasionally be associated with HCP, but more often merely represents expansion of the third ventricle and separation of the lateral ventricles)
   B. septo-optic dysplasia: *see page 247*

SIGNS AND SYMPTOMS OF ACTIVE HCP

In young children

1. cranium enlarges at a rate > facial growth
2. irritability, poor head control, N/V
3. fontanelle full and bulging
4. enlargement and engorgement of scalp veins: due to reversal of flow from intracerebral sinuses due to increased intracranial pressure[23]
5. **Macewen's sign**: cracked pot sound on percussing over dilated ventricles
6. 6th nerve (abducens) palsy: the long intracranial course is postulated to render this nerve very sensitive to pressure
7. "setting sun sign" (upward gaze palsy): **Parinaud's syndrome** from pressure on region of suprapineal recess (*see page 114*)
8. hyperactive reflexes
9. irregular respirations with apneic spells
10. splaying of cranial sutures (seen on plain skull x-ray)

In older children/adults with rigid cranial vault

Symptoms of increased ICP, including: papilledema, H/A, N/V, gait changes, upgaze and/or abducens palsy. Slowly enlarging ventricles may initially be asymptomatic.

CHRONIC HCP

Features indicative of *chronic* hydrocephalus (as opposed to acute hydrocephalus):

1. beaten copper cranium (some refer to beaten silver appearance) on plain skull xray[24]. By itself, does not correlate with increased ICP, however when associated with #3 and #4 below, does suggest ↑ ICP. May be seen in

craniosynostosis (*see page 231* for description)
2. 3rd ventricle herniating into sella (seen on CT or MRI)
3. erosion of sella turcica (may be due to #2 above) which sometimes produces an **empty sella**, and erosion of the dorsum sella
4. the temporal horns may be less prominent on CT than in acute HCP
5. **macrocrania**: by convention, OFC greater than 98th percentile[25 (pp 203)]
6. atrophy of corpus callosum: best appreciated on sagittal MRI
7. in infants
   A. sutural diastasis
   B. delayed closure of fontanelles
   C. failure to thrive or developmental delay

OCCIPITAL-FRONTAL CIRCUMFERENCE

The occipital-frontal circumference **(OFC)** should be followed in every growing child (as part of a "well-baby" check-up, and especially in infants with documented or suspected hydrocephalus **(HCP)**). As a rule of thumb, the OFC of a normal infant should equal the distance from crown to rump[26] (rule #335). *See page 1206* for the DDx of macrocephaly.

Normal head growth: parallels normal curves as seen on the graphs on the inside front cover, or in *Figure 15-2* and *Figure 15-3* for preemies. Any of the following may signify treatable conditions such as active HCP, subdural hematoma, or subdural effusions, and should prompt an evaluation of the intracranial contents (e.g. CT, head U/S …):

1. upward deviations (crossing curves)
2. continued head growth of more than 1.25 cm/wk
3. OFC approaching 2 standard deviations **(SD)** above normal
4. head circumference out of proportion to body length or weight, even if within normal limits for age (*see Figure 15-3*)[27]

These conditions may also be seen in the "catch-up phase" of brain growth in premature infants after they recover from their acute medical illnesses, see *Catch-up phase of brain growth* page 1136). Deviations below the curves or head growth in the premature infant in the neonatal period of less than 0.5 cm/wk (excluding the first few weeks of life) may indicate microcephaly (*see page 245*).

Technique: measure circumference around forehead and occiput (excluding ears) three consecutive times, and use the largest value. OFC is then plotted on a

graph of average values as a function of age[28] and followed for each individual patient. Use the graphs on the inside front cover for most children and adolescents. The graph in *Figure 15-2* shows the OFC for premature infants as a function of gestational age up to term.

The graph in *Figure 15-3* shows the relationship of head circumference, weight and length for various gestational ages.

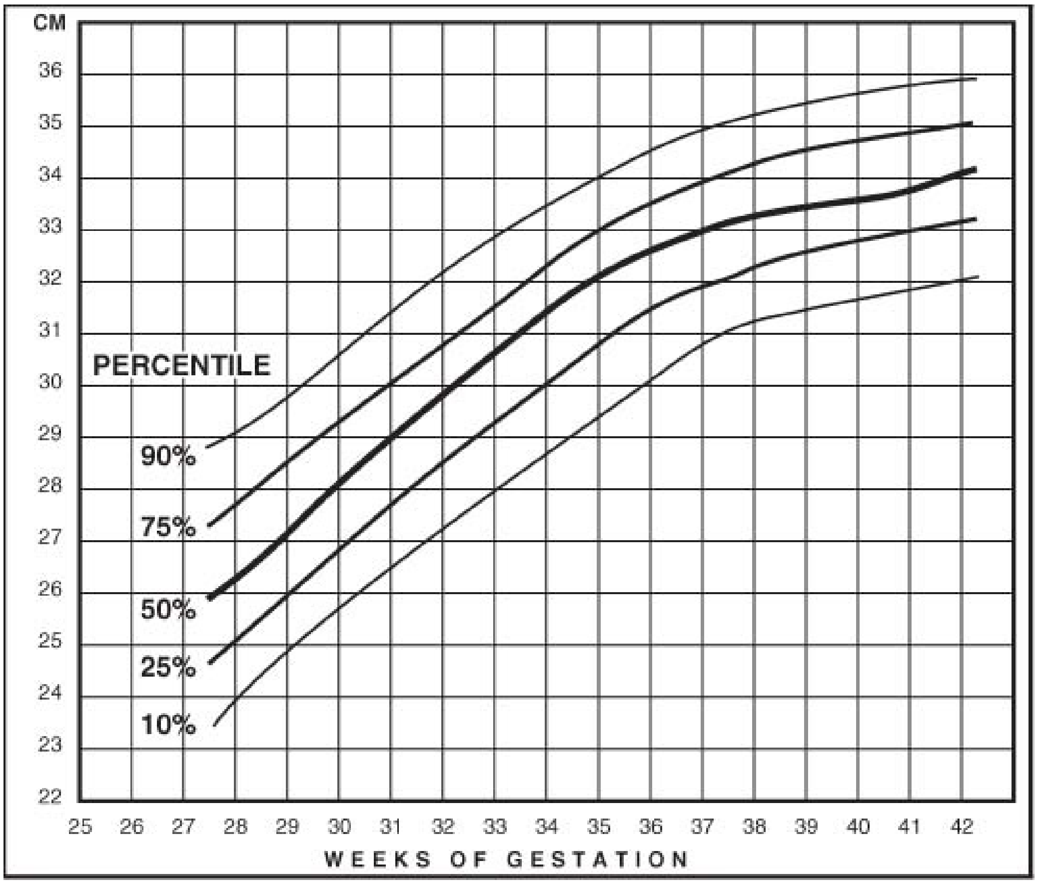


Figure 15-2 OFC for premature infants as a function of gestational age

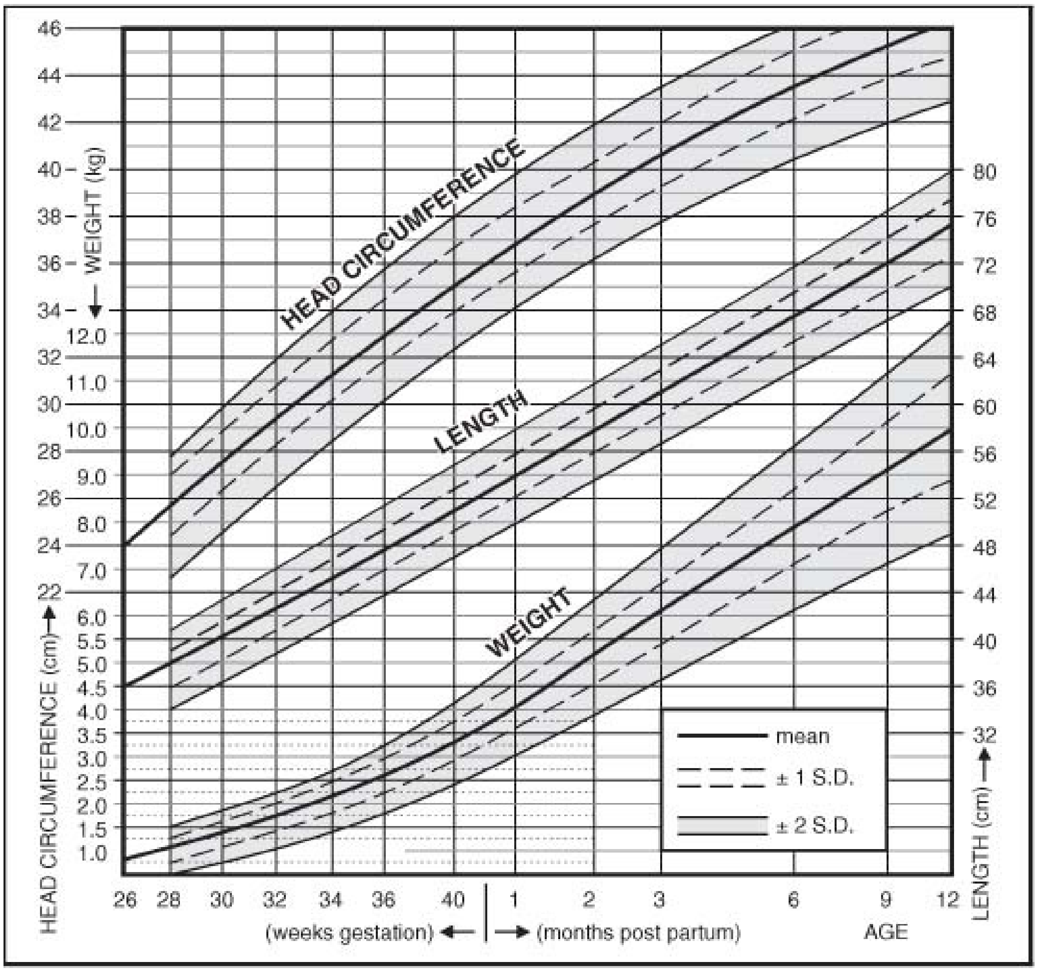


Figure 15-3 Head circumference, weight and length*

*(Redrawn from **Journal of Pediatrics**, "Growth Graphs for the Clinical Assessment of Infants of Varying Gestational Age", Babson S G, Benda G I, vol 89, pp 815, with permission)

15.1. Treatment of hydrocephalus

MEDICAL

HCP remains a surgically treated condition. Acetazolamide may be helpful for temporizing (*see below*).

Diuretic therapy

May be tried in premature infants with bloody CSF (as long as there is no evidence of active hydrocephalus) while waiting to see if there will be

resumption of normal CSF absorption. However, at best this should only be considered as an adjunct to definitive treatment or as a temporizing measure.

Satisfactory control of HCP was reported in ≈ 50% of patients of age < 1 year who had stable vital signs, normal renal function and no symptoms of elevated ICP (apnea, lethargy, vomiting) using the following[29]:

- **acetazolamide** (a carbonic anhydrase inhibitor): 25 mg/kg/day PO divided TID **x** 1 day, increase 25 mg/kg/day each day until 100 mg/kg/day is reached
- simultaneously start **furosemide**: 1 mg/kg/day PO divided TID
- to counteract acidosis:
  - ◆ tricitrate (Polycitra®) 4 ml/kg/day divided QID (each ml is equivalent to 2 mEq of bicarbonate, and contains 1 mEq K^+ and 1 mEq Na^+)
  - ◆ measure serial electrolytes, and adjust dosage to maintain serum HCO_3 > 18 mEq/L
  - ◆ change to Polycitra-K® (2 mEq K^+ per ml, no Na^+) if serum potassium becomes low, or to sodium bicarbonate if serum sodium becomes low
- watch for electrolyte imbalance and acetazolamide side effects: lethargy, tachypnea, diarrhea, paresthesias (e.g. tingling in the fingertips)
- perform weekly U/S or CT scan and insert ventricular shunt if progressive ventriculomegaly occurs. Otherwise, maintain therapy for a 6 month trial, then taper dosage over 2-4 weeks. Resume 3-4 mos of treatment if progressive HCP occurs

Spinal taps

HCP after intraventricular hemorrhage may be only transient Serial taps (ventricular or LP[30]) may temporize until resorption resumes (*see page 1135*) but LPs can only be performed for communicating HCP. If reabsorption does not resume when the protein content of the CSF is < 100 mg/dl, then it is unlikely that spontaneous resorption will occur (i.e. a shunt will usually be necessary).

Surgical

Goals of therapy:

Normal sized ventricles is not the goal of therapy. Goals are optimum neurologic function and a good cosmetic result.

Options include:

1. choroid plexectomy: described by Dandy in 1918 for communicating

hydrocephalus[31]. May reduce the rate but does not totally halt CSF production (only a portion of CSF is secreted by the choroid plexus, other sources include the ependymal lining of the ventricles and the dural sleeves of spinal nerve roots). Open surgery was associated with a high mortality rate (possibly due to replacement of CSF by air). Endoscopic choroid plexus coagulation was originally described in 1910 and was recently resurrected[32]

2. eliminating the obstruction: e.g. opening a stenosed sylvian aqueduct. Often higher morbidity and lower success rate than simple CSF diversion with shunts, except perhaps in the case of tumor
3. third ventriculostomy: (*see below*)
4. shunting: various shunts are described below. The techniques of shunt placement are covered on page 209 for VP shunts, page 210 for VA shunt, page 210 for ventriculopleural shunts, and page 213 for LP shunt

Third ventriculostomy

Endoscopic third ventriculostomy **(ETV)** has energized a renewed interest in third ventriculostomy (*see page 212* for technique).

Indications: ETV may be used in patients with obstructive HCP. May be an option in managing shunt infection (as a means to remove all hardware without subjecting the patient to increased ICP). ETV has also been proposed as an option for patients who developed subdural hematomas after shunting (the shunt is removed before the ETV is performed). ETV may also be indicated for slit ventricle syndrome (*see page 326*).

Contraindications: *Communicating* hydrocephalus has traditionally been considered a contraindication to ETV. However, it is used for NPH in some centers[33]. Relative contraindications to ETV would be the presence of any of the conditions associated with a low success rate (*see below*).

Complications:

1. hypothalamic injury
2. transient 3rd and 6th nerve palsies
3. uncontrollable bleeding
4. cardiac arrest[34]
5. traumatic basilar artery aneurysm[35]: possibly related to thermal injury from use of laser in performing ETV

Success rate: Overall success rate is ≈ 56% (range of 60-94% for nontumoral aqueductal stenosis[35] **(AqS)**). Highest maintained patency rate is with previously untreated acquired AqS. Success rate in infants may be poor because they may not have a normally developed subarachnoid space. There is a low success rate (only ≈ 20% of TVs will remain patent) if there is pre-existing pathology including:

1. tumor
2. previous shunt
3. previous SAH
4. previous whole brain radiation (success with focal stereotactic radiosurgery is not known)
5. significant adhesions visible when perforating through the floor of the third ventricle at the time of performance of ETV

In one series, clinical improvement after ETV was achieved in 76% (72 of 95 patients), including 6 patients requiring second ETVs (three of which had partially functioning shunts that were left in place at the time of ETV).

15.1.1. Shunts

For surgical insertion techniques, see *Ventricular shunts* on page 208.

TYPES OF SHUNTS

SHUNT TYPE BY CATEGORY

1. ventriculoperitoneal **(VP)** shunt:
   A. most commonly used shunt in modern era
   B. lateral ventricle is the usual proximal location
   C. intraperitoneal pressure: normal is near atmospheric
2. ventriculo-atrial **(VA)** shunt (“vascular shunt”):
   A. shunts ventricles through jugular vein to superior vena cava, so-called “ventriculo-atrial” shunt because it shunts the *cerebral ventricles* to the vascular system with the catheter tip in the region of the right *cardiac atrium*)
   B. treatment of choice when abdominal abnormalities are present (extensive abdominal surgery, peritonitis, morbid obesity, in preemies who have had NEC and may not tolerate VP shunt…)

C. shorter length of tubing results in lower distal pressure and less siphon effect than VP shunt, however pulsatile pressures may alter CSF hydrodynamics

3. Torkildsen shunt:
   A. shunts ventricle to cisternal space
   B. rarely used
   C. effective only in acquired obstructive HCP, as patients with congenital HCP frequently do not develop normal subarachnoid CSF pathways
4. miscellaneous: various distal projections used historically or in patients who have had significant problems with traditional shunt locations (e.g. peritonitis with VP shunt, SBE with vascular shunts):
   A. pleural space (**ventriculopleural shunt**): not a first choice, but a viable alternative if the peritoneum is not available[36]. To avoid symptomatic hydrothorax necessitating relocating distal end, it is recommended only for patients > 7 yrs age. Pressure in pleural space is less than atmospheric
   B. gall bladder
   C. ureter or bladder: causes electrolyte imbalances due to losses through urine
5. lumboperitoneal (LP) shunt (for insertion technique, *see page 213*):
   A. only for communicating HCP: primarily pseudotumor cerebri or CSF fistula[37]. Useful in situations with small ventricles
   B. over age 2 yrs, percutaneous insertion with Tuohy needle is preferred
6. cyst or subdural shunt: from arachnoid cyst or subdural hygroma cavity, usually to peritoneum

Disadvantages/complications of various shunts

1. those that may occur with any shunt:
   A. obstruction: the most common cause of shunt malfunction
      - proximal: ventricular catheter (the most common site)
      - valve mechanism
      - distal: reported incidence of 12-34%[38]. Occurs in peritoneal catheter in VP shunt (*see below*), in atrial catheter in VA shunt
   B. disconnection at a junction, or break at any point
   C. infection
   D. hardware erosion through skin, usually only in debilitated patients

(especially preemies with enlarged heads and thin scalp from chronic HCP, who lay on one side of head due to elongated cranium). May also indicate silicone allergy (*see below*)

E. <u>seizures</u> (ventricular shunts only): there is ≈ 5.5% risk of seizures in the first year after placement of a shunt which drops to ≈ 1.1% after the 3rd year[39] (NB: this does not mean that the shunt was the cause of all of these seizures). Seizure risk is questionably higher with frontal catheters than with parieto-occipital

F. act as a conduit for extraneural metastases of certain tumors (e.g. medulloblastoma). This is probably a relatively low risk[40]

G. silicone allergy[41]: rare (if it occurs at all). May resemble shunt infection with skin breakdown and fungating granulomas. CSF is initially sterile but later infections may occur. May require fabrication of a custom silicone-free device (e.g. polyurethane)

2. **VP** shunt:

A. 17% incidence inguinal hernia (many shunts are inserted while processus vaginalis is patent)[42]

B. need to lengthen catheter with growth: may be obviated by using long peritoneal catheter (*see page 209*)

C. obstruction of peritoneal catheter:

- may be more likely with distal slit openings ("slit valves") due to occlusion by omentum or by trapping debris from the shunt system[38]
- by peritoneal cyst (or pseudocyst)[43]: usually associated with infection, may also be due to reaction to talc from surgical gloves (the omentum tends to "wall off" a nidus of irritation). It may rarely be necessary to differentiate a CSF collection from a urine collection in patients with overdistended bladders that have ruptured (e.g. secondary to neurogenic bladder). Fluid can be aspirated percutaneously and analyzed for BUN and creatinine (which should be absent in CSF)
- severe peritoneal adhesions: reduce surface area for CSF resorption
- malposition of catheter tip:
    - at time of surgery: e.g. in preperitoneal fat
    - tubing may pull out of peritoneal cavity with growth

D. peritonitis from shunt infection

E. hydrocele

F. CSF ascites

G. tip migration

- into scrotum[44]
- perforation of a viscus[45]: stomach[46], bladder… More common with older spring-reinforced (Raimondi) shunt tubing
- through the diaphragm[47]

H. intestinal *obstruction* (as opposed to perforation): rare

I. volvulus[48]

J. intestinal strangulation: occurred only in patients in whom attempt was made to remove peritoneal tubing using traction on the catheter applied at the cephalad incision with subsequent breakage of the tubing leaving a residual intraabdominal segment (immediate peritoneal exploration is recommended under these circumstances)[49]

K. overshunting: more likely than with VA shunt. Some recommend LP shunt for *communicating* hydrocephalus (*see page 325*)

3. **VA** shunt:

A. requires repeated lengthening in growing child

B. higher risk of infection, septicemia

C. possible retrograde flow of blood into ventricles if valve malfunctions (rare)

D. shunt embolus

E. vascular complications: perforation, thrombophlebitis, pulmonary micro-emboli may cause pulmonary hypertension[50] (incidence ≈ 0.3%)

4. **LP** shunt:

A. if at all possible, should not be used in growing child unless ventricular access is unavailable (e.g. due to slit ventricles) because of:

- laminectomy in children causes scoliosis in 14%[51]
- risk of progressive cerebellar tonsillar herniation (Chiari I malformation)[52] in up to 70% of cases[53, 54]

B. overshunting harder to control when it occurs (a special horizontal-vertical **(H-V)** valve increases resistance when upright, *see below*)

C. difficult access to proximal end for revision or assessment of patency (see *Lumboperitoneal (LP) shunt evaluation*, page 214)

D. lumbar nerve root irritation (radiculopathy)

E. leakage of CSF around catheter

F. pressure regulation is difficult
G. bilateral 6th and even 7th cranial nerve dysfunction from overshunting
H. high incidence of arachnoiditis and adhesions

MISCELLANEOUS SHUNT HARDWARE

1. tumor filter: used to prevent peritoneal or vascular seeding in tumors that may metastasize through CSF (e.g. medulloblastoma[55], PNETs, ependymoma); may eventually become occluded by tumor cells and need replacement; may be able to radiate tumor filter to "sterilize" it. The risk of "shunt mets" appears to be low[40]
2. antisiphon device: prevents siphoning effect when patient is erect
3. "horizontal-vertical valve" (H-V valve) used with LP shunts to increase the valve resistance when the patient is vertical to prevent overshunting (*see page 321*)
4. there are a number of variable pressure valves on the market that may be externally programmed
5. on-off device: used to open or occlude shunt system by using external manipulation of shunt (e.g. Portnoy device)

Programmable shunt valves

3 externally programmable shunts are available in the U.S.: Strata by Medtronic (*page 319*), Polaris by Sophysa (*page 319*), and the Codman Hakim (*page 320*). All are programmed externally with a magnet, and can potentially be inadvertently reprogrammed by external magnetic fields including that encountered during an MRI (the Polaris valve may be less susceptible to inadvertent reprogramming *see page 319*).

★ Therefore, valve settings should be rechecked after an MRI scan performed for any reason, or if there is ever a concern about shunt function. The pressure setting on all of these valves can be checked on a plain x-ray taken perpendicular to the shunt valve (see the section in this book for each shunt for interpretation), the Strata and Polaris can also be checked using a special hand-held compass-like device provided by the manufacturer to most hospitals and clinics that deal with their valves.

In all 3 systems, increasing the programmed number results in higher valve pressures and therefore less CSF drainage at any given CSF pressure.

SHUNT TYPE BY MANUFACTURER

Numerous shunt systems are on the market. The following describes the salient features of some commonly used shunts. Diagrams are not to scale.

X-RAY APPEARANCE OF SOME SHUNTS

The following figure depicts idealized x-ray appearances of some common shunts.

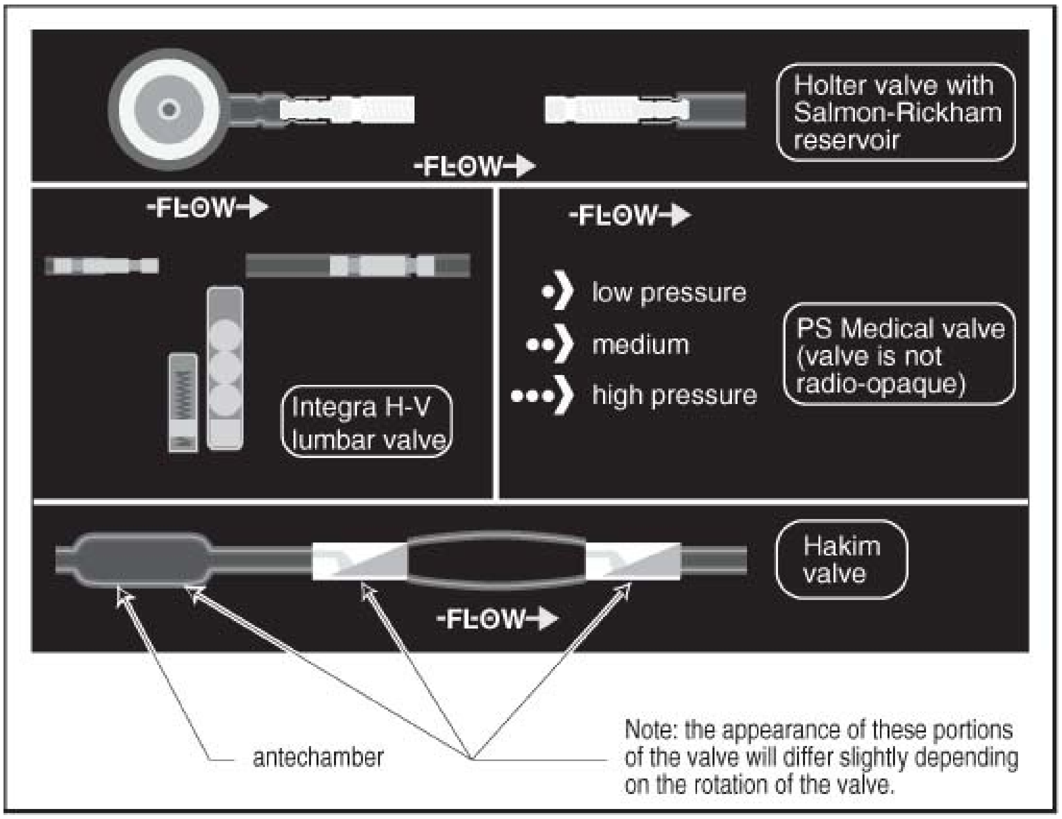


Figure 15-4 X-ray appearance of common shunts For x-ray appearance of programmable valves and the corresponding pressures, see the individual valve.

PS MEDICAL/MEDTRONIC

Medtronic
125 Cremona Dr.
Goleta, CA 93117 USA
(800) 826-5603
www.medtronic.com

Standard contoured valve

A single one-way membrane valve design. The radioopaque arrowhead points in the direction of flow (*see Figure 15-4*).

Pumping the valve

To pump the shunt in the "forward" direction, first occlude the inlet port (*see Figure 15-6*) with pressure from one finger on the "inlet occluder" (prevents back-flow into the ventricle during the next step). Then while maintaining this pressure, depress the reservoir dome with a second finger. Release both fingers, and repeat. The oneway valve regulates shunt pressure and prevents reflux of CSF during normal use and during the release phase of shunt pumping.

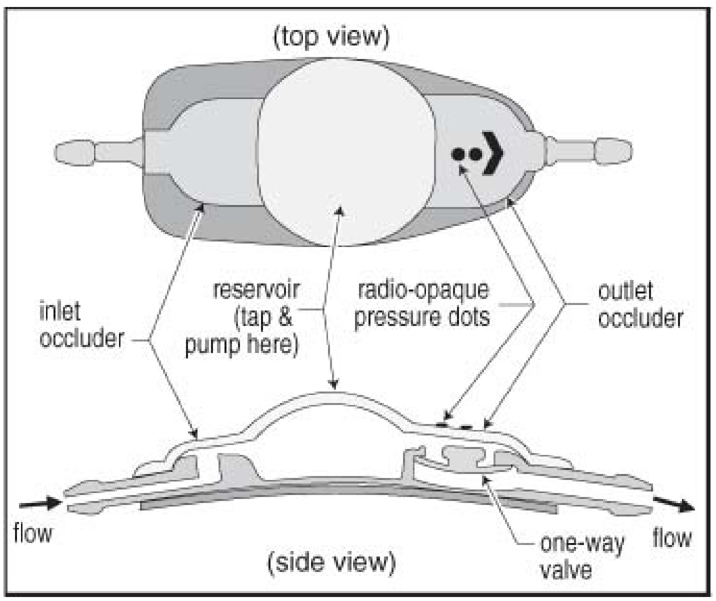


Figure 15-5 PS Medical standard contoured valve

X-ray characteristics

The three available valve pressures are indicated by radioopaque dots on the valve (allows x-ray identification of valve pressure): one dot = low pressure, two dots = medium, three dots = high.

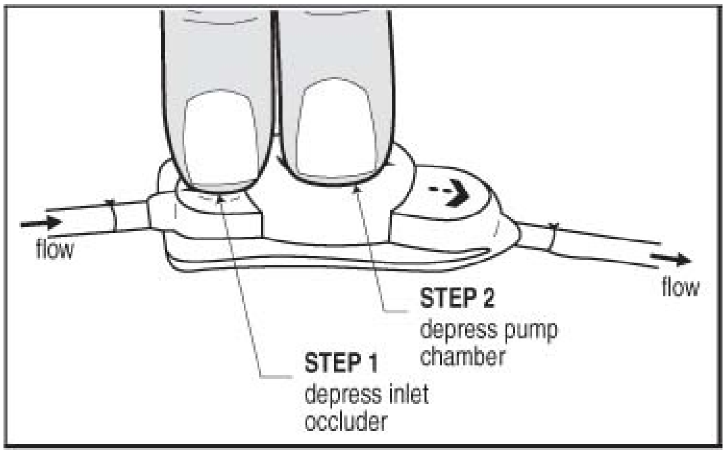


Figure 15-6 Pumping the PS Medical valve

Strata® programmable valve

The Medtronic Strata valve is an externally adjustable valve that is programmed (using a magnet) to one of five performance level ("P/L") settings (*Figure 15-7*).

Also, see general information regarding programmable valves on *page 317*.

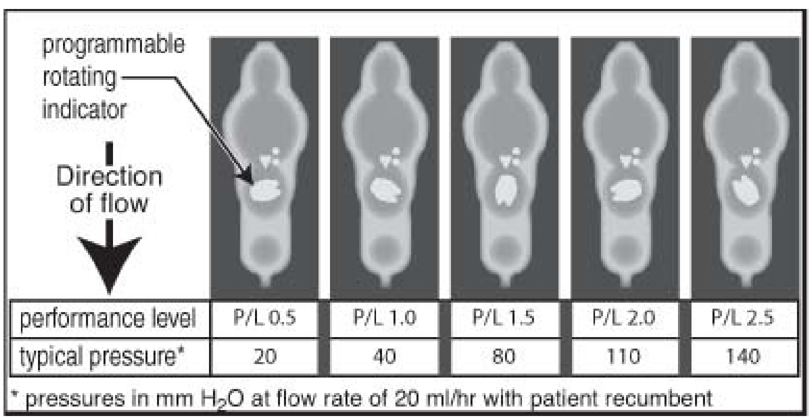


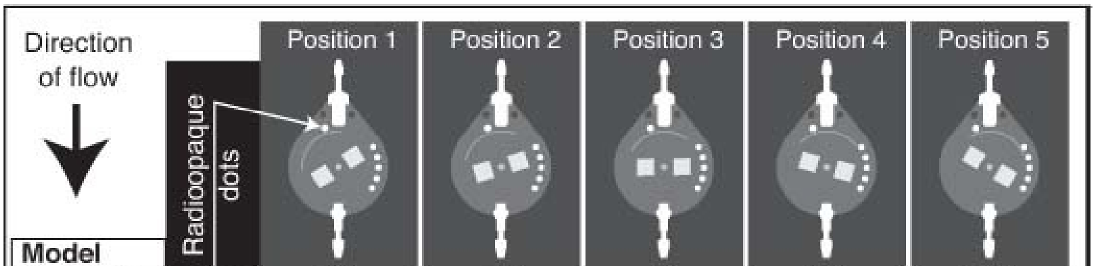
Figure 15-7 Performance level (P/L) settings for the regular size Strata valve as seen on x-ray

Sophysa USA

Sophysa USA, Inc.
1620 Sunflower Ave
Costa Mesa, CA 92626 USA
(714) 429-8801
www.sophysa.com

Polaris programmable valve

The Polaris valve is an externally programmable valve that uses two attracting Samarium-Cobalt magnets to lock the pressure setting and to resist inadvertent reprogramming by environmentally encountered magnets such as MRI scanners, cell phones, headphones…



Model	Radioopaque dots	Position 1	Position 2	Position 3	Position 4	Position 5
SPV-140	none	10	40	80	110	140
SPV A or B	●	30	70	110	150	200
SPV-300	●●	50	100	150	220	300
SPV-400	●●●	80	150	230	330	400

Figure 15-8 Programmable settings for Polaris valve models as seen on x-ray (pressures in mm H_2O)

Available in 4 models (different pressure ranges, each identified by a unique number of radioopaque dots), each with 5 externally adjustable positions. The x-ray appearance and corresponding pressures are shown in *Figure 15-8*.

CODMAN

Codman
325 Paramount Dr.
Raynham, MA 02767 USA
(800) 225-0460
www.codman.com

Codman Hakim programmable valve

18 pressure settings. Programmed by an AC-powered programming unit that requires confirmatory x-ray after reprogramming. Newer programming units with acoustic monitoring may obviate the need for x-ray. The manufacturer advises not to increase the pressure by > 40 mm H_2O in a 24-hour period.

X-ray appearance for various settings are shown in *Figure 15-9* (note:

settings of 70, 120 & 170 mm H_2O align with an arm of the central cross of the valve). NB: when x-rayed correctly, the x-ray beam passes first through the valve and then the patient, which causes the radioopaque marker to appear as a solid circle to the right of center as shown in *Figure 15-9*. If the marker is on the left side, the beam is passing from the bottom of the valve, and the actual pressure reading should be based on a mirror image of the x-ray.

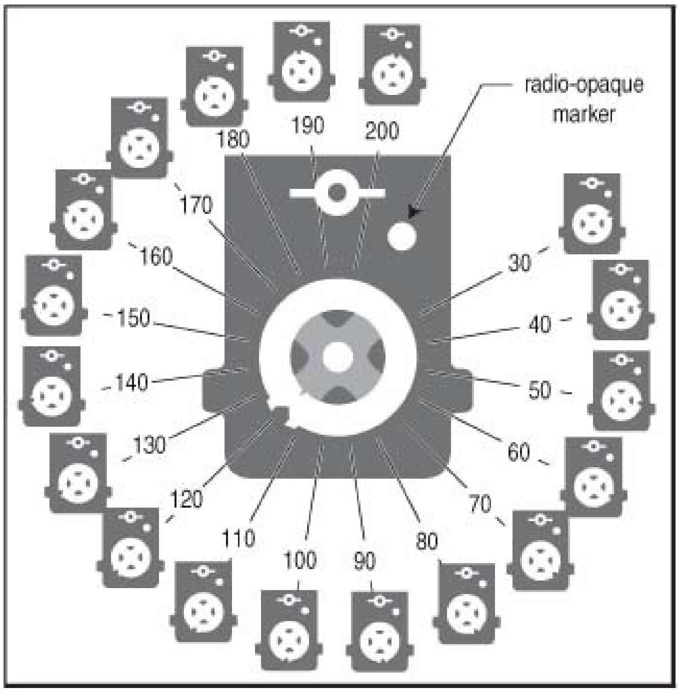


Figure 15-9 X-ray appearance of Codman Hakim programmable valve at it's various settings in mm Hg (e.g. the large central image shows a setting of 120 mm H_2O)

NeuroCare

Distributed in U.S. by:
NeuroCare Group
8401 102nd Street
Suite 200
Pleasant Prairie, WI 53158
(800) 997-4868

Heyer-Schulte

The LPV valve is shown in *Figure 15-10*. To pump the shunt, occlude inlet

port with one finger, then depress reservoir with another finger (as for the PS Medical valve, *see above*). This valve may be injected in either direction by depressing the appropriate occluder while injecting into the reservoir.

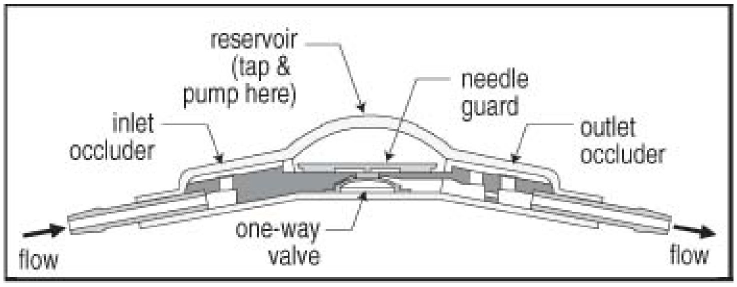


Figure 15-10 Heyer-Schulte LPV® (low-profile) valve (side view)

HAKIM SHUNT

Distributed by:
Integra Neurosciences
In the U.S.:
311 Enterprise Drive
Plainsboro, NJ 08536
(800) 654-2873
http://www.integra-ls.com

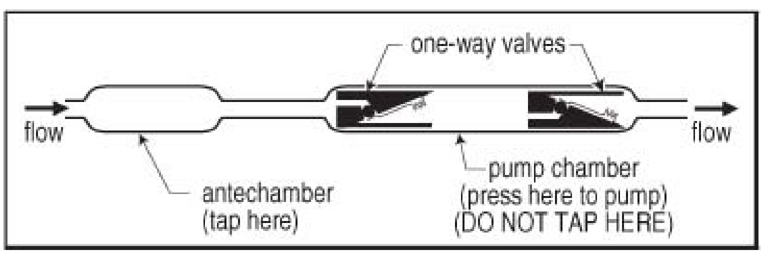


Figure 15-11 Hakim Standard Mechanism

A dual ball-valve mechanism. To pump shunt, depress the indicated portion of the valve. NB: do not tap here, as the silicone elastomer housing is not self-sealing. The antechamber is provided for this type of access.

INTEGRA (CORDIS) HORIZONTAL-VERTICAL LUMBAR VALVE

May be used in lumboperitoneal shunt to increase the transmission pressure when the patient is upright to prevent overshunting. Markings used to orient the

device during implantation:

1. an arrow on the inlet side of the unit indicates direction of flow
2. inlet tubing is clear
3. inlet tubing has smaller diameter than outlet tubing
4. outlet tubing is white
5. before positioning the valve and fastening it to the fascia with permanent suture, the valve should be connected to both the subarachnoid catheter (inlet) and the peritoneal catheter (outlet). The arrow on the inlet valve should point towards the patient's feet

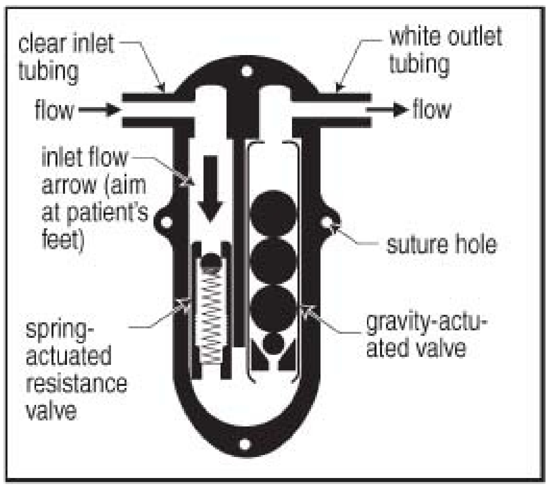


Figure 15-12 Cordis H-V valve

Holter valve

A dual slit valve mechanism (*see Figure 15-13*). Usually used in combination with a Rickham or Salmon-Rickham reservoir (*see Figure 15-14*).

To pump the shunt, simply depress the indicated portion of the valve.

X-ray characteristics

The silastic tube between the two one-way valves is radiolucent (see *Figure 15-4*, page 318).

Salmon-Rickham reservoir

Similar to standard Rickham reservoir except for lower profile (*see Figure 15-14*).

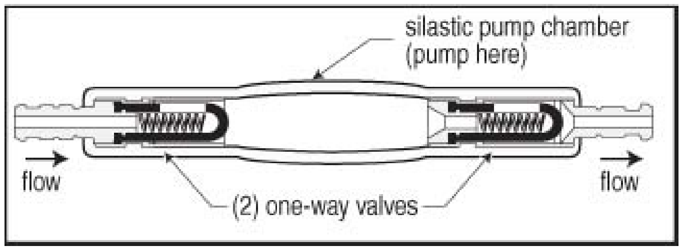


Figure 15-13 Holter valve

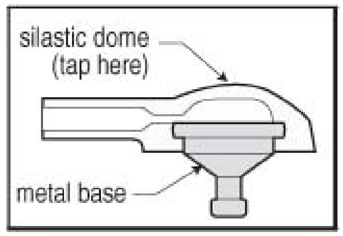


Figure 15-14 Salmon-Rick-ham Reservoir

15.2. Shunt problems

15.2.1. Problems associated with shunt insertion

1. intraparenchymal or intraventricular hemorrhage: ≈ 4% (in the absence of coagulopathy 56)
2. seizures
3. malposition
   A. of ventricular catheter
   B. of distal catheter
4. infection

15.2.2. Problems in patients with established CSF shunt

Shunt “problems” usually involve one or more of the following:

1. undershunting (*see below*): obstruction rate: ≈ 10% per year } accounts for most common shunt problems
2. infection (*see* *page 345*): range 1-40%. A serious complication. Having a

shunt infection decrease IQ } accounts for most common shunt problems

3. overshunting: slit ventricle syndrome, subdural hematomas… (*see page 325*)
4. seizures: *see page 316*
5. problems related to the distal catheter
   A. peritoneal: *see page 316*
   B. atrial: *see page 317*
6. skin breakdown over hardware: infection or silicone allergy (*see page 316*)
7. hemorrhage at time of insertion: uncommon in pediatrics

TAPPING A SHUNT

Indications to tap a shunt or ventricular access device (e.g. Ommaya reservoir) include:

1. to obtain CSF specimen
   A. to evaluate for shunt infection
   B. for cytology: e.g. in PNET to look for malignant cells in CSF
   C. to remove blood: e.g. in intraventricular hemorrhage
2. to evaluate shunt function
   A. measuring pressures
   B. contrast studies:
      1. proximal injection of contrast (iodinated or radiolabeled)
      2. distal injection of contrast
3. as a temporizing measure to allow function of a distally occluded shunt[57, 58]
4. to inject medication
   A. antibiotics: for shunt infection or ventriculitis
   B. chemotherapeutic (antineoplastic) agents
5. for catheters placed within tumor cyst (not a true shunt):
   A. periodic withdrawal of accumulated fluid
   B. for injection of radioactive liquid (usually phosphorous) for ablation

TECHNIQUE

Table 15-2 Steps in tapping a shunt

Step	Information provided
1. insert needle into reservoir and look for spontaneous flow into butterfly tubing; measure pressure in manometer	• spontaneous flow indicates proximal end not completely occluded • pressure is that of ventricular system (should be < 15 cm of CSF in relaxed recumbent patient)
2. also measure the pressure with distal occluder pressed if present	• rise in pressure indicates some function of valve and distal shunt
3. if no spontaneous flow, try to aspirate CSF with syringe	• if CSF is easily aspirated, it may be that pressure seen by ventricular system is near 0 • if no CSF obtained or if difficult to aspirate, indicates proximal occlusion
4. send CSF for: C&S, protein/glucose, cell count	• checks for infection
5. fill manometer with sterile saline, & occlude <u>proximal</u> (inlet) occluder (with Holter valve, tap the valve itself, although this is not recommended because the hole thus created may not seal)	• measures forward transmission pressure (through valve and peritoneal catheter in presence of shunt with proximal occluder); forward pressure should be less than ventricular pressure
6. repeat measurement after injecting 3-5 ml of saline	• if peritoneal catheter is in a loculated compartment the pressure will be considerably higher after injection

[(For LP shunt, see *Lumboperitoneal (LP) shunt evaluation*, page 214).

There is a risk of introducing infection with every entry into the shunt system. With care, this may be kept to a minimum.

1. shave area
2. povidone iodine solution prep **x** 5 minutes
3. use 25 gauge butterfly needle or smaller (ideally a noncoring needle should be used): for routine taps, the needle should only be introduced into shunt components specifically designed to be tapped

To measure pressures

Steps are outlined in *Table 15-2*.

INSTRUCTIONS TO PATIENTS

All patients and families of patients with hydrocephalus should be instructed regarding the following:

1. signs and symptoms of shunt malfunction or infection
2. not to pump the shunt unless instructed to do so for a specific purpose
3. prophylactic antibiotics: for the following situations (mandatory in vascular shunts, sometimes recommended in other shunts)
   A. dental procedures
   B. instrumentation of the bladder: cystoscopy, CMG, etc.
4. in a growing child: the need for periodic evaluation, including assessment

of distal shunt length

UNDERSHUNTING

The shunt malfunction rate is ≈ 17% during the first year of placement in the pediatric population.

May be due to one or a number of the following:

1. blockage (occlusion)
   A. possible causes of occlusion:
      1. obstruction by choroid plexus
      2. buildup of proteinaceous accretions
      3. blood
      4. cells (inflammatory or tumor)
      5. secondary to infection
   B. site of blockage
      1. blockage of ventricular end (most common): usually by choroid plexus, may also be due to glial adhesions, intraventricular blood
      2. blockage of intermediate hardware (valves, connectors, etc., tumor filters may become obstructed by tumor cells, antisiphon devices may close due to variable overlying subcutaneous tissue pressures[59])
      3. blocked distal end (*see page 316* for VP shunt)
   C. disconnection, kinking or breakage of system at any point: with age, silicone elastomers used in catheters calcify and break down, and become more rigid and fragile which may promote subcutaneous attachment[60]. Barium impregnation may accelerate this process. Tube fractures often occur near the clavicle, presumably due to the increased motion there

Signs and symptoms of undershunting

Signs and symptoms are those of active hydrocephalus, and include:

1. acute <u>symptoms</u> of increased intracranial pressure
   A. H/A
   B. N/V
   C. diplopia
   D. lethargy

E. ataxia
F. infants: apnea and/or bradycardia; irritability
G. seizures: new onset, increase in frequency, or difficulty in control

2. acute signs of increased intracranial pressure
   A. upward gaze palsy ("setting sun sign", see *Parinaud's syndrome*, page 114)
   B. abducens palsy: false localizing sign
   C. field cut, or blindness (see *Blindness from hydrocephalus*, page 335)
   D. papilledema (rare before age 2 yrs)
   E. infants: bulging fontanelle, prominent scalp veins
3. swelling around shunt tubing: caused by CSF dissecting along shunt tract
4. chronic changes: before sutures close, OFCs crossing curves

EVALUATION OF SHUNT FOR UNDERSHUNTING

1. history and physical directed at determining presence of above signs and symptoms, also ascertain:
   A. reason for initial insertion of shunt (MM, post-meningitis, etc.)
   B. date of last revision and reason for revision
   C. presence of accessory hardware in system (e.g. antisiphon device, etc.)
   D. for children: OFC. Plot on graph of normal curves (use existing chart for that patient if available)
   E. fontanelle tension (if open): a soft pulsating fontanelle varying with respirations is normal, a tense bulging fontanelle suggests obstruction, a sunken fontanelle may be normal or may represent overshunting
   F. ability of shunt to pump and refill
      1. caution: may exacerbate obstruction, especially if shunt is occluded by ependyma due to overshunting: controversial
      2. difficult to depress: suggests distal occlusion
      3. slow to refill (generally, any valve should refill in 15-30 secs): suggests proximal (ventricular) occlusion
   G. evidence of CSF dissecting along tract outside of shunt tubing
   H. in children presenting only with vomiting, especially those with cerebral palsy and feeding gastrostomy tubes, rule-out gastroesophageal reflux
2. radiographic evaluation
   A. "shunt series" (plain x-rays to visualize entire shunt: for VP shunt, AP & lateral skull + "low" CXR and/or abdominal x-ray)

1. R/O disconnection or migration of tip by x-rays to visualize entire shunt; note: a disconnected shunt may continue to function by CSF flow through a fibrous tract; the following hardware may be radiolucent and can mimic disconnection:
   a. the central silastic part of a Holter style valve
   b. connectors ("**Y**" & "**T**" as well as straight)
   c. antisiphon devices
   d. tumor filters
2. obtain most recent x-rays available to compare for breaks (essential for "complicated" shunts involving multiple ventricular or cyst ends or accessory hardware)

B. in patients with open fontanelles, ultrasound is optimal method of evaluation (especially if previous U/S available)

C. CT required if fontanelles closed, may be desirable in complicated shunt systems (e.g. cyst shunts)

D. MRI: shunt hardware is difficult to see. May show transependymal absorption of CSF, loculations…

E. "shunt-o-gram" if it is still unclear if shunt is functioning
   1. radionuclide: *see below*
   2. x-ray: using iodinated contrast: *see below*

3. shunt tap: indications vary, generally performed if surgical exploration is considered or if infection is strongly suspected (see *Tapping a shunt*, page 322)

4. shunt exploration: sometimes even after thorough evaluation the only means to definitively prove or disprove the functioning of various shunt components is to operate and isolate and test each part of the system independently. Even when infection is not suspected, CSF and any removed hardware should be cultured.

"Shunt-o-gram"

Procedure: shave hair over reservoir & prep with Betadine. With patient supine tap the shunt by inserting a 25 gauge butterfly needle into the reservoir. Measure the pressure with a manometer. Patients with multiple ventricular catheters need to have each injected to verify its patency.

Radionuclide "shunt-o-gram" AKA radionuclide shuntography[61]: after tapping the shunt, drain 2-3 ml of CSF and send 1 ml of CSF for C&S. Inject radio-isotope (e.g. for VP shunt in an adult, use 1 mCi of 99m-Tc (technetium)

pertechnetate (usable range: 0.5 to 3 mCi) in 1 cc of fluid) while occluding distal flow (by compressing valve or occluding ports). Flush in isotope with remaining CSF.

Immediately image the abdomen with the gamma camera to rule out direct injection into distal tubing. Image the cranium to verify flow into ventricles (proximal patency). If spontaneous flow into abdomen is not seen after 10 minutes the patient is sat up and res-canned. If flow is not seen after 10 minutes, then the shunt is pumped. Look for diffusion of the isotope within the abdomen to rule out pseudocyst formation around catheter.

X-ray "shunt-o-gram": after tapping the shunt, drain ≈ 1 ml of CSF and send for C&S. Inject e.g. iohexol (Omnipaque 180) (*see page 122*) while occluding distal flow (by compressing valve or occluding ports).

PSEDUOCYST (PERITONEAL) WITH VP SHUNT

Usually a marker for infection.

Treatment algorithm

One of many viable surgical protocols to deal with this:

1. open abdominal incision over tubing, and divide tubing at this site
2. verify which cut end is the peritoneal end and which is the distal shunt (with a working shunt, pumping the valve should cause CSF to come out the distal shunt)
3. attempt to drain the cyst through the remaining peritoneal end
    A. when you can't draw any more fluid, or if you don't get any to begin with, withdraw the catheter a little at a time and aspirate at each step
    B. send any fluid obtained for culture
    C. if tubing does not pull out smoothly, the abdomen may need to be opened (consider consulting general surgeon)
4. verify function of remaining shunt
    A. if the remaining shunt is functioning
        1. connect it to sterile collection system
        2. monitor output volumes & send surveillance cultures of CSF qod
        3. after 3 consecutive cultures are negative, internalize distal end of shunt (using fresh distal catheter). The choice of target for distal end (peritoneum, pleura, vein) depends on whether abdominal cyst fluid is infected and if the peritoneal cavity still seems suitable)
    B. if the shunt is not functioning, a new external ventricular catheter

should be inserted and connected to a collection system

1. monitor output volumes & send surveillance cultures of CSF qod
2. after 3 consecutive cultures are negative, remove the old shunt and place a totally shunt. The choice of target for distal end (peritoneum, pleura, vein) depends on whether abdominal cyst fluid is infected and if the peritoneal cavity still seems suitable)

SHUNT INFECTION

See *Shunt infection* on page 345 for evaluation and treatment.

"OVERSHUNTING"

POSSIBLE COMPLICATIONS OF OVERSHUNTING INCLUDE[62]

1. slit ventricles: including slit ventricle syndrome (*see below*)
2. intracranial hypotension: *see below*
3. subdural hematomas: *see page 327*
4. craniosynostosis and microcephaly: controversial (*see page 328*)
5. stenosis or occlusion of sylvian aqueduct

10-12% of long-term ventricular shunt patients will develop one of the above problems within 6.5 yrs of initial shunting[62]. Some experts feel that problems related to over-shunting could be reduced by utilizing LP shunts for communicating hydrocephalus, and reserving ventricular shunts for obstructive HCP[62]. VP shunts may also be more likely to overdrain than VA shunts because of the longer tubing → greater siphoning effect.

INTRACRANIAL HYPOTENSION

AKA low ICP syndrome. Very rare. Symptoms similar to those of spinal H/A (postural in nature, relieved by recumbency). Although usually not associated with the following symptoms[63], they may occur[62]: N/V, lethargy, or neurologic signs (e.g. diplopia, upgaze palsy). Sometimes the symptoms resemble those of high ICP except that they are relieved when prostrate. Acute effects that may occur include[62]: tachycardia, loss of consciousness, other brain stem deficits due to a rostral shift of the intracranial contents or to low ICP.

Etiology is a siphoning effect due to the column of CSF in the shunt tube when the patient is erect[64]. Ventricles may be slit-like (as in slit ventricle

syndrome **(SVS)**) or may be normal in appearance. Sometimes it is necessary to document a drop in ICP when going from supine to erect to diagnose this condition. These patients may also develop shunt occlusion and then the distinction from SVS blurs (*see below*).

With short-term symptoms, an ASD is the treatment of choice. However, patients with long-standing overshunting may not tolerate efforts to return intraventricular pressures to normal levels[62, 65].

SLIT VENTRICLES

"Slit ventricles" refers to complete collapse of the ventricles. In a survey, a frontal-occipital horn ratio[19] < 0.2 was most often interpreted as representing SVS. May be seen in:

1. overshunting
2. with entrapped (isolated) fourth ventricle: *see page 309*
3. some patients with idiopathic intracranial hypertension (AKA pseudotumor cerebri) (*see page 713*) have slit-like ventricles with consistently elevated ICP

May be one of the following:

1. asymptomatic:
   A. slit ventricles (totally collapsed lateral ventricles) may be seen on CT in 3 -80% of patients after shunting[63, 66], most are asymptomatic
   B. these patients may occasionally present with symptoms unrelated to the shunt, e.g. true migraine
2. **slit ventricle syndrome (SVS)**: seen in < 12% of all shunted patients. Subtypes:
   A. intermittent shunt occlusion: overshunting leads to ventricular collapse (slit ventricles) which causes the ependymal lining to occlude the inlet ports of the ventricular catheter (by coaptation) producing shunt obstruction. With time, many of these patients develop low ventricular compliance[67], where even minimal dilatation results in high pressure which produces symptoms. Expansion then eventually reopens the inlet ports allowing resumption of drainage (hence the intermittent symptoms). Symptoms may resemble shunt malfunction: intermittent headaches unrelated to posture, often with N/V, drowsiness, irritability and impaired mentation. Signs may include 6th cranial nerve palsy. Incidence in shunted patients: 2-5%[63, 68]. CT or MRI scans may also show evidence of transependymal absorption of

CSF

B. total shunt malfunction (AKA normal volume hydrocephalus[67]): may occur and yet ventricles remain slit-like if the ventricles cannot expand because of subependymal gliosis, or due to the law of Laplace (which states that the pressure required to expand a large container is lower than the pressure required to expand a small container)

C. venous hypertension with normal shunt function: may result from partial venous occlusion that occurs in some conditions (e.g. at the level of the jugular foramen in Crouzon's syndrome). Usually subsides by adulthood

3. intracranial hypotension: symptoms often relieved by recumbency (*see above*)

EVALUATION OF SLIT VENTRICLES

The shunt valve fills slowly if pumped when the ventricles are collapsed.

Monitoring CSF pressure: either via lumbar drain, or with a butterfly inserted into the shunt reservoir (with this method, pressure can be followed during postural changes to look for negative pressure when upright; possibly higher risk of infection with this). These patients are also monitored for pressure spikes, especially during sleep.

Alternatively, these patients may be evaluated by "shunt-o-gram" (*see above*).

TREATMENT

In treating a patient with slit ventricles in imaging studies, it is important to ascertain into which of the categories (*see above*) the patient falls. If the patient can be categorized, then the specific treatment listed below should be employed. Otherwise, it is probably most common to initially treat the patient empirically as intracranial hypotension, and then to move on to other methods for treatment failures.

Asymptomatic slit ventricles

Prophylactic upgrading to a higher pressure valve or insertion of an antisiphon device has largely been abandoned. However, this may be appropriate at the time of shunt revision when done for other reasons[66].

Intracranial hypotension

Postural H/A due to intracranial hypotension (true overshunting) is usually self limited, however, if symptoms persist after ≈ 3 days of bed-rest and analgesics and a trial with a tight abdominal binder, the valve should be checked for proper closing pressure. If it is low, replace with a higher pressure valve. If it is not low, an **antisiphon device (ASD)** (which, by itself, also increases the resistance of the system) alone or together with a higher pressure valve may be needed[69].

Slit ventricle syndrome

Patients with symptoms of SVS are actually suffering from intermittent *high* pressure. If total shunt malfunction is the cause, then shunt revision is indicated. For intermittent occlusion, treatment options include:

1. if symptoms occur early after shunt insertion or revision, initial expectant management may be indicated since symptoms will spontaneously resolve in many
2. revision of the proximal shunt. This may be difficult due to the small size of the ventricles. One can attempt to follow the existing tract and insert a longer or shorter length of tubing based on the pre-op imaging studies. Some advocate the placement of a second ventricular catheter, leaving the first one in place
3. patients may "respond" to either of the following interventions because the slight ventricular enlargement elevates the ependyma off of the inlet ports:
   A. valve upgrade[70] or
   B. ASD insertion[63, 69]: the procedure of choice in some opinions[62]. First described in 197371
4. subtemporal decompression[72-74] sometimes with dural incision[72]. This results in dilatation of the temporal horns (evidence for elevated pressure) in most, but not all[74] cases
5. third ventriculostomy[75]: *see page 315*

Problems unrelated to shunting

For H/A consistent with migraine that are not postural, a trial with migraine-specific medications is warranted (Fiorinal®…). For treatment of idiopathic intracranial hypertension (pseudotumor cerebri), *see page 717*.

SUBDURAL HEMATOMAS

May be due to collapse of brain with tearing of bridging veins. In the pre-CT era, the incidence of subdural hematoma **(SDH)** formation following shunt insertion was probably underestimated at ≈ 1.2%. However, more recent estimates are 4-23% in adults, 2.8-5.4% in children, and is higher with normal pressure hydrocephalus (20-46%) than with "hypertensive hydrocephalus" (0.4-5%)[76, 77]. The risk of SDH is higher in the setting of longstanding hydrocephalus with a large head and little brain parenchyma (craniocerebral disproportion) with a thin cerebral mantle, as usually occurs in children with macrocephaly and large ventricles on initial evaluation. These patients have an "extremely delicate balance between subdural and intraventricular pressure"[76]. SDH can also follow shunting in elderly patients who have severe brain atrophy. The development of SDH may also be facilitated by negative pressures in the ventricles as a result of siphoning[77, 78]. There is also a low risk of epidural hematoma following CSF shunting[77].

Characteristics of the fluid: The collections may be on the same side as the shunt in 32%, on the opposite side in 21%, and bilateral in 47%[77].

At the time of discovery, the SDHs are usually subacute to chronic, and the previously large ventricles are usually collapsed. Only 1 of 19 cases showed colorless fluid[77]. In all cases tested, protein was elevated compared to CSF.

TREATMENT

Indications for treatment

Small (< 1-2 cm thick) asymptomatic collections in patients with closed cranial sutures may be followed with serial imaging. SDH were symptomatic in ≈ 40% of cases (symptoms often resemble those of shunt malfunction), and these require treatment. Treatment of SDH in children with open sutures has been advocated[77] to prevent later symptoms and/or development of macrocrania. Many authors recommend not treating asymptomatic lesions regardless of appearance[76, 79], whereas others vary their recommendations based on diverse criteria including size, appearance (chronic, acute, mixed…), etc.

Treatment techniques

A number of techniques have been described. Most involve evacuation of the SDHs by any of the usual methods (e.g. burr holes for chronic collections, craniotomy for acute collections) together with:

1. reducing the degree of shunting (i.e. to establish a lower pressure in the subdural space than in the intraventricular space, to cause the ventricles to re-expand and to prevent reaccumulation of the SDH)
   A. in shunt dependent cases
      1. replacing the valve with a higher pressure unit (upgrading the valve)
      2. increasing the pressure on a programmable pressure valve[80, 81]
      3. using a Portnoy device that can be turned off and on externally. Be sure that care providers can reliably open the device in an emergency
   B. in non-shunt dependent cases
      1. any of the methods outlined above for shunt dependent cases, or
      2. temporarily tying off the shunt[82]
   C. insertion of an anti-siphon device[71]
2. drainage of the subdural space to
   A. the cisterna magna[83]
   B. to the peritoneum with a low pressure valve (or no valve[77]). Some authors have the care-giver frequently pump the subdural valve

The goal is to achieve a delicate balance between undershunting (producing symptoms of active hydrocephalus) and overshunting (promoting the return of the SDH). Following surgery the patient should be mobilized slowly to prevent recurrence of the SDH.

MISCELLANEOUS SHUNT ISSUES

CRANIOSYNOSTOSIS, MICROCEPHALY & SKULL DEFORMITIES

Also see *Craniosynostosis*, page 228. A number of skull changes have been described in infants after shunting, including[84]: thickening and inward growth of the bone of the skull base and cranial vault, decrease in size of the sella turcica, reduction in size of the cranial foramina, and craniosynostosis. The most common skull deformity was dolichocephaly from sagittal synostosis[85]. Microcephaly accounted for ≈ 6% of skull deformities after shunting (about half of these had sagittal synostosis). Some of these changes were reversible (except when complete synostosis was present) if intracranial hypertension recurred.

LAPAROSCOPIC SURGERY IN PATIENTS WITH VP SHUNTS

Issues regarding safety of laparoscopic surgery in patients with VP shunts:

1. laparoscopic surgery: abdominal insufflation with CO_2 is used to create a pneumoperitoneum permitting the general surgeon to work. Typical insufflation pressure: 15 mm Hg (*see page 870* for conversion factors between mm Hg and cm of water). In thin patients, 10 mm Hg may suffice. Transient additional increases in pressure may occur, e.g. when the surgeon leans on the patient's abdomen
2. concerns for patients with VP shunts:
   A. in some cases insufflation → ↑ ICP[86] which may be due to:
      1. compression of vena cava → reduced venous return from head, as in valsalva maneuver (independent of presence of a shunt)
      2. absorption of CO_2 from the peritoneum → ↑ in arterial CO_2 causing cerebral arterial dilatation thereby increasing ICP (*see page 880*)
      3. ↓ CSF drainage due to ↑ pressure against which CSF must flow
      4. retrograde passage of air/debris into intracranial compartment through an incompetent shunt valve (this also has potential for infection in the presence of peritonitis). This risk is minimal even with in vitro back-pressures up to 80 mm Hg[87]. Retrograde flow may also occur with a valveless shunt (rarely used)
      - in one case report monitoring TCDs[88], there was no change during laparoscopic surgery in a patient with a VP shunt (except during periods of very high pressure)
   B. occlusion of the distal catheter by air, debris[89] or soft tissue
   C. extremely high intraabdominal pressures (> 80 mm Hg in vitro) may damage the valve[87], which could cause malfunction after the laparoscopy

Prophylactic management options:

1. very controversial, special precautions may not be necessary[90]
2. one can temporarily occlude the peritoneal catheter (e.g. by a hemoclip applied by the general surgeon through the laparoscope under minimal initial insufflation pressure; the clip is removed at the end of the procedure), or, temporary externalization of the shunt by the neurosurgeon, with internalization at the end of the procedure (this engenders an increased risk of infection)
3. ICP monitoring during laparoscopy
4. using low insufflation pressures (e.g. < 10 mm Hg)

15.3. Normal pressure hydrocephalus

Key concepts:

- triad (not pathognomonic): dementia, gait disturbance, urinary incontinence
- communicating hydrocephalus on CT or MRI
- normal pressure on random LP
- symptoms may be remediable with CSF shunting

Normal pressure hydrocephalus **(NPH)**, AKA Hakim-Adams syndrome, first described in 196591, is clinically important because it may cause treatable symptoms, including one of the few forms of remediable dementia.

As originally described, the hydrocephalus of NPH was considered to be idiopathic. However, in some cases a predisposing condition (“secondary NPH”) may be identified:

1. post-SAH
2. post-traumatic
3. post-meningitis
4. following posterior fossa surgery
5. tumors, including carcinomatous meningitis
6. also seen in ≈ 15% of patients with Alzheimer’s disease **(AD)**
7. deficiency of the arachnoid granulations
8. aqueductal stenosis may be an overlooked cause

It is becoming increasingly acknowledged that the ventricular enlargement is likely not the underlying pathologic entity. Interest persists in effects such as impaired pulsatility. The search continues to improve the understanding of this complicated condition.

Table 15-3 Comparison of cognitive deficits in Alzheimer’s disease (AD) and NPH*†

Feature	AD	NPH
memory	↓	± auditory memory
executive function‡	↓	±
attention concentration	↓	±
orientation	↓	
writing	↓	

learning	↓	
fine motor speed and accuracy	±	↓
psychomotor skills	±	slowed
language and reading	±	
behavioral or personality changes		±

* modified[94]

† Key: ↓ = impaired; ± = borderline impaired

‡ see Table 15-6 for definition of executive function

CLINICAL

Clinical triad[92]

The triad is not pathognomonic, and similar features may also be seen e.g. in vascular dementia[93], Alzheimer's dementia and Parkinson's disease.

1. gait disturbance: usually precedes other symptoms. Wide based with short, shuffling steps and unsteadiness on turning. Patients often feel like they are "glued to the floor" (so-called "magnetic gait") and may have difficulty initiating steps or turns. Absence of appendicular ataxia
2. dementia: primarily memory impairment with bradyphrenia (slowness of thought) and bradykinesia (*Table 15-3* shows some differentiating features with Alzheimer's disease)
3. urinary incontinence: usually unwitting (NB: a patient demented for any reason or with mobility impairment may have incontinence)

Other clinical features

Age usually > 60 yrs. Slight male preponderance. Also see *Diagnosis* below for other clinical information.

True aphasia is unusual, but speech output may be disturbed by impaired motivation or executive dysfunction[94]. As NPH progresses, cognitive impairment may become more generalized and less responsive to treatment[94]. Symptoms identical to those of idiopathic parkinsonism may occur in 11%[95].

Case reports of a variety of psychiatric disturbances associated with NPH include: depression[96], bipolar disorder[97], aggressiveness[98], paranoia[99].

Symptoms <u>not</u> expected with NPH: Although a variety of clinical features

have been demonstrated to occur infrequently (e.g. SIADH[100], syncope…), clinical features not expected solely as a result of NPH include: papilledema, seizures (prior to shunting), headaches[94].

Differential diagnosis

Table 15-4 shows conditions with presentations similar to findings in NPH in the differential diagnosis[94, 101]. *Table 15-5* compares some features of NPH, Alzheimer's disease, and Parkinson's disease.

Table 15-4 Conditions with similar presentation to NPH

Neurodegenerative disorders • Alzheimer's disease • Parkinson's disease • Lewy body disease • Huntington's disease • frontotemporal dementia • corticobasal degeneration • progressive supranuclear palsy • amyotrophic lateral stenosis • multisystem atrophy • spongiform encephalopathy
Vascular dementia • cerebrovascular disease • multi-infarct dementia • Binswanger's disease • CADASIL • vertebrobasilar insufficiency (VBI)
Other hydrocephalic disorders • aqueductal stenosis • arrested hydrocephalus • long-standing overt ventriculomegaly syndrome • noncommunicating hydrocephalus
Infectious disease • Lyme disease • HIV • syphilis
Urological disorders • urinary tract infection • bladder or prostate cancer • benign prostatic hypertrophy (BPH)
Miscellaneous • vitamin B_{12} deficiency • collagen vascular diseases • epilepsy • depression • traumatic brain injury

• spinal stenosis
• Chiari malformation
• Wernicke’s encephalopathy
• carcinomatous meningitis
• spinal cord tumor

Table 15-5 Comparison of NPH, Alzheimer’s & Parkinson’s disease*

Feature	NPH	AD	IPA
gait disturbance†	+	±	±
postural instability	±		+
urinary disturbance	±	±	±
memory or cognitive impairment	±	+	±
difficulty performing familiar tasks	±	+	±
behavioral changes	±	+	±
limb rigidity			+
limb tremor			+
bradykinesia			+

* abbreviations: AD + Alzheimer’s disease; IPA = idiopathic paralysis agitans (Parkinson’s disease); + = feature present; ± = feature partial or late

† in NPH, the gait is often wide based, in IPA often narrow stance

DIAGNOSIS

PRACTICE GUIDELINE 15-1 DIAGNOSIS OF NPH

Level II[94]: Since strict diagnostic criteria cannot be formulated for NPH because of a lack of knowledge of the underlying pathophysiology at this time, it is recommended that the diagnosis be made in terms of *Probable*, *Possible*, and *Unlikely NPH* as described in *Table 15-6*

Table 15-6 Diagnostic guidelines for NPH[94]

PROBABLE NPH

History*: must include:
1. insidious onset (vs. acute)
2. onset age ≥ 40 years
3. duration ≥ 3-6 months
4. no antecedent head trauma, ICH, meningitis or other known cause of secondary hydrocephalus
5. progression over time
6. no other neurological, psychiatric or general medical conditions that are sufficient to explain the presenting symptoms

Brain imaging: CT or MRI after onset of symptoms

1. ventricular enlargement not attributable to cerebral atrophy or congenital enlargement (Evan's index[†] > 0.3 or comparable measure)
2. no macroscopic obstruction to CSF flow
3. ≥ 1 of the following supportive features
   A. enlarged temporal horns not entirely attributable to hippocampal atrophy
   B. callosal angle ≥ 40°
   C. evidence of altered brain water content, including periventricular changes not attributable to microvascular, ischemic changes, or demyelination
   D. aqueductal or 4th ventricle flow void on MRI

Other imaging findings that may support *Probable* designation but are not required:
1. pre-morbid study showing smaller or nonhydrocephalic ventricles
2. radionuclide cisternogram showing delayed clearance of radiotracer over the convexities after 48-72 hours
3. cine-MRI or other technique showing increased ventricular flow rate
4. SPECT showing decreased periventricular perfusion that is not altered by acetazolamide challenge

Physiological

CSF opening pressure **(OP)** on lateral decubitus LP: 5-18 mm Hg (70-245 mm H_2O)

Clinical: must show gait/balance disturbance, plus impairment in cognition and/or urinary function

1. **gait/imbalance**: ≥ 2 of the following (not entirely attributable to other conditions
   A. decreased step height
   B. decreased step length
   C. decreased cadence (speed of walking)
   D. increased trunk sway while walking
   E. widened standing base
   F. toes turn outward while walking
   G. retropulsion (spontaneous or provoked) must show:
   H. *en bloc* turning (≥ 3 steps to turn 180°)
   I. impaired walking balance: ≥ 2 corrections out of 8 tandem steps
2. **cognition**: documented impairment (adjusted for age & education) and/or decrease in performance on cognitive screening instrument (e.g. Monumental State examination), or evidence of ≥ 2 of the following not fully attributable to other conditions:
   A. psychomotor slowing (increased response latency)
   B. decreased fine motor speed
   C. decreased fine motor accuracy
   D. difficulty dividing or maintaining attention
   E. impaired recall, especially for recent events
   F. executive dysfunction: e.g. impairment in multistep procedures, working memory, formulation of abstractions/similarities, insight
   G. behavioral or personality changes
3. **urinary dysfunction**:
   A. any one of the following
      1. episodic or persistent incontinence not attributable to primary urological disorder
      2. persistent urinary incontinence
      3. urinary and fecal incontinence
   B. or, any 2 of the following:
      1. urinary urgency: frequent perception of a pressing need to void
      2. ↑ urinary frequency (pollakiuria): voiding > 6 times in 12 hours with normal fluid intake
      3. nocturia: needing to void > 2 times in an average night

POSSIBLE NPH

History: reported symptoms may:

1. have subacute or indeterminate mode of onset
2. onset at any age after childhood
3. duration: < 3 months or indeterminate
4. may follow events such as mild head trauma, remote history of ICH, or childhood or adult meningitis or other conditions judged not likely to be causally related
5. coexist with other neurological, psychiatric, or general medical disorders but judged not to be entirely attributable to these conditions

6. be nonprogressive or not clearly progressive	
Clinical: symptoms of either: 1. incontinence and/or cognitive impairment in the absence of observable gait/balance disturbance 2. gait disturbance or dementia alone	
Brain imaging: ventricular enlargement consistent with hydrocephalus but associated with any of the following: 1. cerebral atrophy of sufficient severity to potentially explain ventricular enlargement 2. structural lesions that may influence ventricular size	
Physiological OP not available or outside of the range delineated for *Probable NPH*	
UNLIKELY NPH	
1. no ventriculomegaly 2. signs of increased ICP (e.g. papilledema) 3. no component of the clinical triad of NPH 4. symptoms explained by other causes (e.g. spinal stenosis)	

* history should be verified by individual familiar with premorbid and current condition

† see page 310 for definition and illustration of Evan's index

LUMBAR PUNCTURE (LP) - "TAP TEST"

Opening pressure: Normal LP opening pressure **(OP)** in the left lateral decubitus position averages 12.2 ± 3.4 cm H_2O (8.8 ± 0.9 mm Hg)[102] and should be < 180 mm H_2O[A]. In NPH the average OP is 15 ± 4.5 cm H_2O (11 ± 3.3 mm Hg), slightly higher than, but overlapping with, normal. Based on expert opinion, an upper limit of **24 cm H_2O** (17.6 mm Hg) is suggested for the definition of NPH. Patients with an initial OP > 10 cm H_2O have a higher response rate to shunting.

Tap test: The tap test has not undergone rigorous prospective evaluation. A positive response[B] to withdrawal of 40-50 ml of CSF has a PPV in the range of 73-100%[104-106], but sensitivity is low (26-61%).

Send CSF for routine labs (*see page 203*).

RESISTANCE TESTING

CSF Ro is considered to be the impedance of CSF absorptive mechanisms. 1/Ro is the conductance. Techniques and thresholds are center-specific. No clinical study has adequately addressed the fact that Ro normally increases with age[107].

Determination of CSF Ro may have a higher sensitivity (57-100%) but a similar PPV (75-92%) to the tap test.

Methodology

Numerous methods have been devised to measure Ro. Two illustrative methods:

1. bolus method[108]: inject ≈ 4 ml via LP at a rate of 1 ml/sec
2. Katzman test[109]: infuse saline through LP at a known rate, Ro is given by *Eq 15-1* (up to 19% of patients experience H/A after infusion studies[110])

$$\mathrm{Ro} = \frac{(\text{final steady state pressure}) - (\text{initial pressure})}{\text{infusion rate}} \qquad \textbf{Eq 15-1}$$

AMBULATORY LUMBAR DRAINAGE[104] (ALD)

A lumbar subarachnoid drain is placed with Tuohy needle, connected through a drip chamber to a closed drainage system (*see* *page 202*). The drip chamber is placed at the level of the patient's ear when recumbent, or at the level of the shoulder when sitting or ambulating.

A properly functioning drain should put out ≈ 300 ml of CSF per day.

If symptoms of nerve root irritation develop during the drainage, the catheter should be withdrawn several millimeters. Daily surveillance CSF cell counts and cultures should be performed (NB: a pleocytosis of ≈ 100 cells/mm^3 is expected just with the presence of the drain).

A 5 day trial is recommended (mean time to improvement: 3 days).

CONTINUOUS CSF PRESSURE MONITORING

Some patients with normal OP on LP demonstrate pressure peaks > 270 mm H_2O or recurrent B-waves[111]. These patients may have a higher response rate to shunting.

CT AND MRI

Features on CT[112] and MRI[113]

1. prerequisite: communicating hydrocephalus
2. features that correlate with favorable response to shunt (these features suggest that the hydrocephalus is <u>not</u> due to atrophy alone[C]):
   A. periventricular low density on CT or high intensity on T2WI MRI: may represent transependymal absorption of CSF. May resolve with shunting
   B. compression of convexity sulci (*focal* sulcal dilation may sometimes

be seen and may represent atypical reservoirs of CSF which may diminish after shunting and should not be considered as atrophy[115])

C. rounding of the frontal horns

A. OP > 24 cm H_2O suggests noncommunicating hydrocephalus rather than NPH[94, 103]

B. what constitutes a "significant response" has not been standardized, most experts prefer demonstrating objective improvement in gait, taking into account the fact that NPH patients can have day-to-day fluctuations in symptoms

C. atrophy (hydrocephalus ex vacuo), as in conditions such as Alzheimer's disease, lessens the chance of, but does not preclude, responding to a shunt (cortical atrophy is a common finding in healthy individuals of advanced age[114])

Although some patients improve with no change in ventricles[116], clinical improvement most often accompanies reduction of ventricular size.

Radionuclide cisternography

Usefulness remains controversial. One study found that the cisternogram does not increase the diagnostic accuracy of clinical and CT criteria[117].

Technique: Lumbar subarachnoid injection of radio-isotope (e.g. 2.7 mCi of ^{99m}Tc-DTPA diluted to 1 cc with saline). Cisternograms are obtained by planar scintigraphy at 3, 6, and 24 hrs after injection (images may be obtained at 48 hrs if intraventricular activity is still seen at 24 hrs, however, an isotope other than ^{99m}Tc-DTPA must be used for such delayed images).

Conventional criteria for a normal study: Radioactivity is symmetrically distributed over the convexity 24 hrs after injection, with no intraventricular activity at any point. However, up to 41% of normals will demonstrate transient (up to 24 hrs, but not longer) activity in the ventricles[118].

Findings that may indicate a better chance for response to shunting: Of the following, only #2 is a reliable marker for NPH.

1. early scan (4-6 hrs after injection): activity in ventricles (presumed reflux from obstructed outflow). May also occur in normals (*see above*) for < 24 hrs
2. late scan (48-72 hrs): persistence of ventricular activity. Patients with this finding are most likely to improve with shunting (≈ 75% chance)
3. retained activity over convexity: these patients are less likely to improve

4. quantitative cisternography
   A. patients who clear over 50% of total intracranial radioactivity within 24 hrs are considered to have an adequate overall absorption rate, and are unlikely to improve with shunting. However others have found no correlation of clearance to shunt response
   B. one study found that if the ratio of ventricular to total intracranial activity (V/T) at 24 hours is > 32%, there would be a response to shunting, whereas V/T < 32% did not exclude the possibility of improvement[119]

Miscellaneous

Cerebral blood flow (CBF) measurements: Although some studies indicate otherwise, CBF measurements show no specific findings in NPH, and are not helpful in predicting who will respond to shunting. However, increased CBF after shunting correlates with clinical improvement[120].

EEG: No specific findings on EEG in NPH.

Treatment

Management algorithm

1. based on history, physical exam, and imaging studies, categorize as probable, possible, or unlikely NPH based on *Table 15-6*, page 331. For *probable* and *possible* NPH, without further testing, the degree of certainty of the diagnosis of NPH is ≈ 50-61%[117, 121, 122]. In an otherwise healthy patient in whom the diagnosis of NPH seems highly probable, it is not unreasonable to proceed to shunting[103]
2. otherwise, to increase the certainty of response to shunting, one or more of the following tests is recommended[103]
   A. "tap test": withdrawal of 40-50 ml of CSF via LP
      1. positive response (*see page 332*) increases likelihood of responding to a shunt (PPV) to the range of 73-100%
      2. due to low sensitivity (26-61%), a negative response does not rule out the possibility of responding, and a subsequent supplemental test should be performed[103]
      3. if OP > 17.6 mm Hg (24 cm H_2O), consider further search for cause of secondary hydrocephalus (does not rule-out shunting as a treatment)

B. resistance testing: sensitivity (57-100%) > tap test, similar PPV (75-92%)
C. external lumbar drainage

CSF DIVERSIONARY PROCEDURES

VP shunt is the procedure of choice. Lumbar-peritoneal shunts have been used, but disadvantages include: tendency to overshunt, difficult to tap, tendency to migrate. For most, use a medium pressure valve[123] (closing pressure 65-90 mm H_2O) to minimize the risk of subdural hematomas (*see below*), although response rate may be higher with a low-pressure valve[124]. Gradually sit patient up over a period of several days; proceed more slowly in patients who develop low-pressure headaches. Alternatively, the risk of developing SDH may be decreased with use of a programmable shunt valve, set initially at a high pressure (to reduce risk of subdural hematoma) and gradually decreasing the pressure setting over a number of weeks.

Follow patients clinically and with CT for ≈ 6-12 months.

Patients who do not improve and whose ventricles do not change should be evaluated for shunt malfunction. If not obstructed, a lower pressure valve should be tried (or a lower pressure selected on a programmable shunt).

Endoscopic third ventriculostomy (ETV): Initially reported for NPH in 1999125. Mechanistically, it is difficult to explain why ETV would work for NPH, but it has been advocated by some[33] in highly selected patients, using nonvalidated outcome measures, quoting post-op improvement in 69% of patients. At this time, ETV should not be considered a first line treatment for most cases of NPH.

POTENTIAL COMPLICATIONS OF SHUNTING FOR NPH

Complication rates may be as high as ≈ 35% (due to the frailty of the elderly brain)[126, 127].

Potential complications include[128]:

1. subdural hematomas or hygroma (also *see page 327*): higher risk with low pressure valve and older patients who tend to have cerebral atrophy. Usually accompanied by headache, most resolve spontaneously or remain stable. Approximately one third require evacuation and tying off of shunt (temporarily or permanently). Risk may be reduced by gradual mobilization post-op

2. shunt infection
3. intracerebral hemorrhage
4. seizures: *see page 316*
5. delayed complications include: above, plus shunt obstruction or disconnection

OUTCOME

The most likely symptom to improve with shunting is incontinence, then gait disturbance, and lastly dementia. Black et al.[123] give the following markers for good candidates for improvement with shunting:

- clinical: presence of the classic triad[126] (*see page 329*). Also 77% of patients with gait disturbance as the primary symptom improved with shunting. Patients with dementia and no gait disturbance rarely respond to shunting
- LP: OP > 100 mm H_2O
- isotope cisternogram: typical NPH pattern. The mixed or normal pattern has no correlation with response to shunting
- continuous CSF pressure recording: pressure > 180 mm H_2O or frequent Lundberg B waves (*see page 872*)
- CT or MRI: large ventricles with flattened sulci (little atrophy)

Response is better when symptoms have been present for a shorter time.

NB: NPH patients with co-existing Alzheimer's disease **(AD)** may still improve with VP shunts, thus AD should not exclude these patients from shunting[129]. However, patients with AD alone did not respond to shunting in a RPDB placebo-controlled trial[130].

Some responders may subsequently deteriorate. Shunt malfunction and subdural collections must be ruled out before ascribing this to the natural course of the condition.

15.4. Blindness from hydrocephalus

A rare complication of hydrocephalus and/or shunt malfunction. Possible causes include:

1. occlusion of posterior cerebral arteries **(PCA)** caused by downward transtentorial herniation

2. chronic papilledema causing injury to optic nerve at the optic disc

3. dilatation of the 3rd ventricle with compression of optic chiasm

Ocular motility or visual field defects are more common with shunt malfunction than is blindness[131-134]. One series found 34 reported cases of permanent blindness in children attributed to shunt malfunction with concomitant increased ICP[135] (these authors were based in a referral center for visually impaired children, thus incidence not estimated). Another series of 100 patients with tentorial herniation (most from acute EDH and/or SDH) proven by CT; 48 patients operated; only 19 of 100 survived > 1 month (all were in operated group); 9 of 100 developed occipital lobe infarct (2 died, 3 vegetative state, remaining 4 moderate to severe disability)[136].

TYPES OF VISUAL DISTURBANCE

9 of 14 had pregeniculate (anterior visual pathway) blindness with marked optic nerve atrophy (early), and reduced pupillary light reflexes. 5 of 14 had postgeniculate (cortical) blindness with normal light responses and minimal or no optic nerve atrophy (or atrophy late). A few patients had evidence of damage in both sites.

Cortical blindness: due to lesions posterior to lateral geniculate bodies **(LGB)**, may also be seen with hypoxic injuries or trauma[137]. Occasionally associated with **Anton's syndrome** (denial of visual deficit) and with Ridoch's phenomenon (appreciation of moving objects without perception of stationary stimuli).

PATHOPHYSIOLOGY

In patients with occipital lobe infarction

Occipital lobe infarctions **(OLI)** in PCA distribution are seen either bilaterally, or if unilateral are associated with other injuries to optic pathways posterior to LGB. The most often cited mechanism is compression of PCA resulting from brain herniating downward. Alternatively, upward cerebellar herniation (e.g. from ventricular puncture in face of a p-fossa mass) may impinge on PCA or branches with the same results[138].

OLIs are more likely with a rapid rise in ICP (doesn't allow compensatory shifts and collateral circulation to develop)[139]. Macular sparing is common.

Reported causes of OLI include: post traumatic edema, tumor, abscess, SDH, unshunted hydrocephalus, and shunt malfunction[140-142].

The occipital poles are also particularly vulnerable to diffuse hypoxia[143]; attested to by cases of cortical blindness after cardiac arrest[144]. Hypotension superimposed on compromised PCA circulation (from herniation or elevated ICP) may thus increase the risk of postgeniculate blindness[135, 139].

Both coup and contrecoup trauma may produce OLI. Unlike a PCA occlusion infarct, macular sparing is not expected in traumatic occipital lobe injury[140].

In patients with pregeniculate blindness

Elevated ICP transmits pressure to retina → bloodflow stasis, as well as mechanical trauma to optic chiasm from enlarging third ventricle (latter more commonly thought to be responsible for bitemporal hemianopia[131], but could, if unchecked, progress to complete visual loss). Also, if hypotension and anemia were present, consider the possibility of ischemic optic neuropathy[145-147] which may be anterior, or posterior (the latter of which carries a poorer prognosis).

Presentation

These deficits are frequency unsuspected (altered mental state and the youth of many of these patients[135] makes detection difficult); an examiner must persevere to detect homonymous hemianopsias in an obtunded patient[140].

Pregeniculate blindness is less often associated with depressed sensorium than is postgeniculate (where direct compression and vascular compromise of midbrain are more likely[135]).

Prognosis

Cortical blindness after diffuse anoxia frequently improves (occasionally to normal); usually slowly (weeks to years quoted; several mos usually adequate)[144]. Many reports of blindness after shunt malfunction are pre-CT era, thus the presence or extent of occipital lobe infarction not ascertained. Some optimistic outcomes reported[148], however, permanent blindness or severe visual handicap are described[140, 142]; no reliable predictor has been identified. As with infarcts elsewhere, younger patients fare better[143], but extensive calcarine infarcts on CT are probably incompatible with significant visual recovery.

15.5. Hydrocephalus and pregnancy

Patients with CSF shunts may become pregnant, and there are at least 4 case reports of patients developing hydrocephalus during pregnancy requiring shunting[149].

With VP shunts, distal shunt problems may be higher in pregnancy. The following are management suggestions modified from Wisoff et al.[149].

Preconception management of patients with shunts

1. evaluation, including:
   A. evaluation of shunt function: preconception baseline MRI or CT. Further evaluation of shunt patency if any suspicion of malfunction. Patients with slit ventricles may have reduced compliance and may become symptomatic with very small changes in volume
   B. assessment of medications, especially anticonvulsants
2. counselling, including:
   A. genetic counselling: if the HCP is due to a neural tube defect **(NTD)**, then there is a 2-3% chance that the baby will have a NTD
   B. other recommendations include early administration of prenatal vitamins, and avoiding teratogenic drugs and excessive heat (e.g. hottubs): see *Neural tube defects, Risk factors* on page 245.

Gravid management

1. close observation for signs of increased ICP: headache, N/V, lethargy, ataxia, seizures… Caution: these signs may mimic pre-eclampsia (which must also be ruled out). 58% of patients exhibit signs of increased ICP, which may be due to:
   A. decompensation of partial shunt malfunction
   B. shunt malfunction
   C. some show signs of increased ICP in spite of adequate shunt function, may be due to increased cerebral hydration and venous engorgement
   D. enlargement of tumor during pregnancy
   E. cerebral venous thrombosis: including dural sinus thrombosis & cortical venous thrombosis
   F. encephalopathy related to disordered autoregulation (*see page 73*)
2. patients developing symptoms of increased ICP should have CT or MRI
   A. if no change from preconception study, puncture shunt to measure ICP and culture CSF. Consider radioisotope shunt-o-gram

B. if all studies are negative, then physiologic changes may be responsible. Treatment is bed rest, fluid restriction, and in severe cases steroids and/or diuretics. If symptoms do not abate, then early delivery is recommended as soon as fetal lung maturity can be documented (give prophylactic antibiotics for 48 hrs before delivery)

C. if ventricles have enlarged and/or shunt malfunction is demonstrated on testing, shunt revision is performed
   1. in first two trimesters: VP shunt is preferred (do not use peritoneal trocar method after first trimester) and is tolerated well
   2. in third trimester: VA or ventriculopleural shunt is used to avoid uterine trauma or induction of labor

Intrapartum management

1. prophylactic antibiotics are recommended during labor and delivery to reduce the incidence of shunt infection. Since coliforms are the most common pathogen in L&D, Wisoff et al. recommend ampicillin 2 gm IV q 6 hrs, and gentamicin 1.5 mg/kg IV q 8 hrs in labor and **x** 48 hrs post partum[149]
2. in patients without symptoms: a vaginal delivery is performed if obstetrically feasible (lower risk of forming adhesions or infection of distal shunt). A shortened second stage is preferred since the increase in CSF pressure in this stage is probably greater than during other valsalva maneuvers[150]
3. in the patient who becomes symptomatic near term or during labor, after stabilizing the patient a C-section under general anesthesia (epidurals are contraindicated with elevated ICP) is performed with careful fluid monitoring (e.g. PA catheter) and, in severe cases, steroids and diuretics

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15.6. References

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NOTES

16. Infections

16.1. Prophylactic antibiotics

General principles[3]

1. antibiotics must be in tissues at time of contamination (thus, avoid "on-call" antibiotics; give 60 minutes prior to incision)
2. repeated administration is vital in prolonged procedures
3. typical infecting organisms are usually predictable. Coverage for these organisms is adequate (broadening spectrum is of no value)
4. in low risk operations (e.g. carotid endarterectomy, where infections rare and seldom life-threatening) may cost more to prevent than to treat
5. prolongation of antibiotics beyond first post-op day provides no additional protection (may not be true in patients with surgical drains)
6. theoretical side effects (alteration of patient's flora, development of resistant strains in patient or hospital) have not been realized without prolonged administration of pre-op or post-op antibiotics
7. factors that increase risk of operative wound infection include:
   A. systemic factors: malnutrition, reoperation, infection at secondary site (especially UTI when GU tract manipulated), prolonged administration of antibiotics
   B. local factors: epinephrine, dehydration, hypoxia

Specific agents for prophylaxis

1. **cephalosporins**:
   A. agents of choice where skin flora (coagulase (–) or (+) staph) are likeliest pathogens
   B. may safely be given even with history of mild, non-immediate manifestations of PCN allergy (e.g. "rashes"). Contraindicated if history of immediate or accelerated reaction (shock, bronchospasm, urticaria)

C. **cefazolin** (Ancef®, Kefzol®):
- effective, widely studied, therapeutic levels in brain tissue after systemic administration[4], long half-life
- prophylactic dose: 1-2 gm (peds: 25 mg/kg up to 1 gm) IV 60 min before surgery, then q 6 hr **x** 24 hrs post-op

D. some *S. aureus* strains are efficient in ß-lactamase degradation of cephalosporins, and cefazolin is particularly susceptible. Lower infection rates may result with cefamandole (2 gm initially, and then 1 gm q 2-3 hrs intraoperatively)[5]

E. a semisynthetic penicillin may be more appropriate if good CSF penetration is necessary

2. **vancomycin**: alternative if cephalosporin contraindicated (incidence of anaphylactic reactions is too high for routine use). Dose (empiric): 15 mg/kg (up to 1 gm) IV pre-op, then 10 mg/kg q 8 hrs for 24 hrs post-op
3. **penicillins**: disadvantages: probably less safe, shorter half-life, may prolong bleeding times. Nafcillin is probably the best agent in this group

PROPHYLACTIC ANTIBIOTICS FOR SPECIFIC NEUROSURGICAL PROCEDURES

1. **carotid endarterectomy**: routine use not indicated (infection risk too low); when risk of infection is high, use cefazolin (as for general prophylaxis, *see above*)
2. **craniotomy**: risk of infection may be increased in prolonged or microsurgical procedures and in reoperations. No significant difference in the specific regimen used was detected in meta-analysis[6]. Options include:
   - cefazolin (*see above*)
   - clindamicin (300 mg IV) pre-op & q 4 hrs
   - vancomycin (*see above*)
   - some add gentamicin (80 mg IM) pre-op to any of these
3. **CSF shunting procedures**: efficacy has been documented when the infection rate is unusually high for some reason (e.g. ≈ 15%). Antibiotics possibly reduce early infections, i.e. ≈ first week post-op

   A. for general use

   1. select one of the following:
      - cefazolin (*see above*)
      - a 1st generation cephalosporin (e.g. cephapirin (Cefadyl®) 25 mg/kg (up to 1 gm)) IVP intra-op and 6 hrs post-op

- nafcillin 50 mg/kg (up to 2 g) IV 60 min before surgery and q 4 hrs post-op **x** 5 doses total

2. PLUS
   - intrathecal gentamicin 4 mg injected into shunt at time of placement (no longer available in U.S., but preservative-free pediatric gentamicin may be diluted appropriately and used)

B. Kaiser: suggests no antibiotics if infection rate low (< 10%). If high (> 20%) use trimethoprim (160 mg IV) plus sulfamethoxazole (800 mg IV) pre-op and q 12 hrs **x** 3 doses post-op (NB: this latter infection rate is very high, and results are thus questionable 7)

4. ICP monitors: *see page 869*
5. procedures involving incisions through **oral or pharyngeal mucosa**: gentamicin (1.7 mg/kg IV) and clindamicin (300 mg IV) pre-op & q 8 hrs post op **x** 24 hrs. Cefazolin & 3rd generation cephalosporin also effective when given over 24 hr period pre-op
6. **spinal surgery**: reduction of infection was *suggested* but was not statistically significant (low incidence would require large study)

A single blind prospective study[7] showed the incidence of post-neurosurgical operative wound infections were reduced with cefazolin (1 gm IV) plus gentamicin (80 mg IV) given one hr before incision and q 6 hrs intra-op (none post-op) with significant results in patients without foreign implants (especially craniotomies; no significant difference for spinal operations, but numbers were small). All infections were *Staph. aureus* or *epidermidis* (makes use of gentamicin questionable).

16.2. Meningitis

Community acquired meningitis **(CAM)** is generally more fulminant than meningitis following neurosurgical procedures (the former tend to occur with more virulent organisms or impaired host defenses). Waterhouse-Friderichsen syndrome: occurs in 10-20% of children with meningococcal infection (usually disseminated infection in age< 10 yrs), produces large petechial hemorrhages in the skin and mucous membranes, fever, septic shock, adrenal failure (due to hemorrhage into adrenal glands) and DIC. Focal neurologic signs are rare in acute purulent meningitis. Meningitis is a medical emergency, and should be treated immediately. See *Lumbar puncture* on page 201 for a discussion about

when to perform an LP.

16.2.1. Post-neurosurgical procedure meningitis

1. usual organisms: *S. aureus*, Enterobacteriaceae, Pseudomonas sp., *pneumococci*
2. empiric antibiotics: vancomycin (to cover MRSA) + ceftazidime specifically: **vancomycin (adult) 1 gm IV q 8 hrs:** (check level before and after 3rd dose and adjust accordingly) + **ceftazidime (Fortaz®) 1-2 gm IV q 8 hrs**
3. for pseudomonas, add gentamicin (IV & IT)
4. if organism turns out to be non-MRSA *S. aureus*, change vancomycin to IV PRSP (e.g. nafcillin)

16.2.2. Post craniospinal trauma meningitis (post-traumatic meningitis)

Epidemiology

Occurs in 1-20% of patients with moderate to severe head injuries[8]. Most cases occur within 2 weeks of trauma, although delayed cases have been described[9]. 75% of cases have demonstrable basal skull fracture (*see page 887*), and 58% had obvious CSF rhinor-rhea.

Pathogens

As expected from above, there is a high rate of infection with organisms indigenous to the nasal cavity. The most common organisms in a series from Greece were Gram-positive cocci (*Staph. hemoliticus*, *S. warneri*, *S. cohnii*, *S. epidermidis*, and *Strep. pneumonia*) and Gram-negative bacilli (*E. coli*, *Klebsiella pneumonia*, *Acinetobacter anitratus*)[8].

Treatment

1. also see *CSF Fistula, Treatment* on page 303
2. antibiotics: appropriate antibiotics are selected based on CSF penetration and organism sensitivities (adapted to the pathogens common in the

patient's locale; in the above series, all Gram-negative strains appeared resistant to ampicillin and third-generation cephalosporins, but were sensitive to imipenem and ciprofloxacin; Gram-positive strains were all sensitive to vancomycin). For empiric antibiotics *see page 343*

3. surgical treatment vs. "conservative treatment": controversial. Some feel that any case of posttraumatic CSF rhinorrhea should be explored[10, 11], and that cases of spontaneous cessation often represent obscuration by incarcerated brain, so-called "sham healing" with the potential for later CSF leak and/or meningitis[9]. Others support the notion that cessation (possibly with the assistance of lumbar spinal drainage) is acceptable
4. continue antibiotics for 1 week after CSF is sterilized. If rhinorrhea persists at this time, surgical repair is recommended

16.2.3. Recurrent meningitis

Patients with recurrent meningitis must be evaluated for the presence of abnormal communication with the intraspinal/intracranial compartment. Etiologies include dermal sinus (either spinal or cranial, *see page 252*), CSF fistula (*see page 300*), or neurenteric cyst (*see page 227*).

16.2.4. Antibiotics for specific organisms in meningitis

Route is IV unless specified otherwise.

- *S. pneumoniae*: PCN G (2nd choice: chloramphenicol)
- *N. meningitidis*: PCN G (2nd choice: chloramphenicol)
- *H. influenza*:
  - A. non-penicillinase producing: ampicillin
  - B. penicillinase producing: chloramphenicol
- Group B strep: ampicillin
- *L. monocytogenes*: ampicillin
- *S. aureus*
  - A. initially before sensitivities known, or if MRSA or multiply resistant strains or resistant coagulase negative *S. aureus* prevalent or suspected: vancomycin + PO rifampin + PO trimethoprim
  - B. once it is known that the staph is not MRSA:
    1. infant (< 7 d): methicillin

2. all others: nafcillin
3. PCN allergy: vancomycin or (cefazolin via both IV + IT)

- aerobic Gram negative rods (GNR)
  A. ceftriaxone, or cefotaxime, or moxalactam (in order of preference, make alterations based on sensitivities)
  B. if aminoglycoside required, intraventricular therapy is indicated after the newborn period
- *P. aeruginosa*
  A. ceftazidime (Fortaz®) alone if not life threatening
  OR
  B. more serious infections require 2 agents (aminoglycoside gives more rapid kill, and may be used initially for 3 days and then stopped if sensitivities to ceftazidime are acceptable): ceftazidime + APAG + IT gentamicin 4 mg q 12 hrs (give via intraventricular route if **ventriculitis** is present)
  OR
  C. for overwhelming infection:
  ceftazidime + tobramicin + ticarcillin
- *candida spp.*
  A. premedicate with the following prior to amphotericin infusion:
    1. IV bolus of NS (e.g. 500 ml) 2 hrs prior to amphotericin infusion to maintain renal blood flow
    2. Demerol 50 mg IV q 1 hr during amphotericin therapy PRN for rigors
    3. acetaminophen 650 mg po or per-NG 30 minutes prior to amphotericin infusion
  B. amphotericin B deoxycholate (not the lipid form) 1 mg/kg IV over 4-6 hr, hold for hypotension (e.g. SBP < 90 mm Hg), cannot be given through peripheral IV because of phlebitis (central line or PICC line needed)
  C. 5-fluorocytosine (5-FC) 25 mg/kg po or per-NG q 6 hrs

16.3. Shunt infection

Risk of early infection after shunt surgery: reported range is 3-20% per procedure (typically ≈ 7%).

Acceptable infection rate[12]: < 5-7% (although many published series have a rate near 20%[13], possibly due to different patient population).

Risk factors for shunt infection

Many factors have been blamed. Some that seem to be better documented include:

1. young age of patient[13]: in myelomeningocele **(MM)** patients, waiting until the child is 2 weeks old may significantly lower the infection rate
2. length of procedure
3. open neural tube defect

Morbidity of shunt infections in children

Children with shunt infections have a increased mortality rate and risk of seizure than those without shunt infection. Those with myelomeningocele who develop ventriculitis after shunting have a lower IQ compared to those without infection[14]. Mortality ranges from 10-15%.

Pathogens

Over 50% of staph infections occur within 2 weeks post-shunt, 70% within 2 mos. Source is often the patient's own skin[12]. It is estimated that in ≈ 3% of operations for shunt insertion the CSF is already infected (therefore culture CSF during insertion).

Early infection

Most commonly:

1. *Staph. epidermidis* (coagulase-negative staph): 60-75% of infections (most common)
2. *S. aureus*
3. Gram-negative bacilli **(GNB)**: 6-20% (may come from intestinal perforation)

In neonates *E. coli* and *Strep. hemoliticus* dominate.

Late infection (> 6 months after procedure)

Risk: 2.7-31% per patient (typically 6%). Almost all *S. epidermidis*. Tends to

be internal type. 3.5% of patients account for 27% of infections[15].

"Late" shunt infections may be due to:

1. an indolent infection due to *Staph. epidermidis*
2. seeding of a vascular shunt during episode of septicemia (probably very rare)
3. colonization from an episode of meningitis

Candida spp. infections

Candida spp. are responsible for the majority of fungal ventricular shunt infections. Usually occurs in children < 1 year age. Incidence: 1-7%[16]. The 4th leading pathogen causing meningitis in neurosurgical patients in 1 study[17], possibly related to the use of prophylactic antibiotics used for ICP monitoring and CSF drainage. Higher incidence in VP shunt patients with abdominal infections and shunts placed in patients with previous bacterial meningitis[18]. CSF typically shows: elevated WBCs and protein, normal glucose. Management recommendations:

1. completely remove the contaminated shunt (may be more important than with bacterial infections)
2. place a fresh external ventricular drain (if patient is shunt dependent)
3. treat with antifungal therapy: *see page 345*
4. place a fresh shunt after ≥ 5-7 days of therapy and clinical response is apparent
5. continue antifungal agents for 6-8 weeks

Presentation

Non-specific syndrome: fever, N/V, lethargy, anorexia, irritability; may mimic acute abdomen. May also present as malfunction; 29% of patients presenting with shunt malfunction had positive cultures. In neonates may manifest as apneic episodes, anemia, hepatosplenomegaly, and stiff neck[19]. *S. epidermidis* infections tend to be indolent (smoldering). GNB infections usually cause more severe illness; abdominal findings more common; main clinical manifestation is fever, usually intermittent and low grade. Erythema and tenderness along shunt tubing occurs occasionally.

Shunt nephritis[20]: may occur with chronic low level infection of a ventriculovascular shunt causing immune complex deposition in renal glomeruli, characterized by proteinuria and hematuria.

Blood tests

WBC: < 10K in one fourth of shunt infections. It is > 20K in one third.

ESR: rarely normal in shunt infections.

Blood cultures: positive in less than one third of cases.

CSF: WBC is usually not > 100 cells/mm^3. Gram stains may be positive ≈ 50% (yield with *S. epidermidis* is much lower). Protein is often elevated, glucose may be low or normal. Rapid antigen tests used for community acquired meningitis are usually not helpful for the organisms that tend to cause shunt infections. CSF cultures are negative in 40% of cases (higher culture yield if CSF WBC count is > 20K).

EVALUATION OF SHUNT FOR INFECTION

1. history and physical directed at determining presence of above signs and symptoms with emphasis on
   A. history suggestive of infection at another site
      1. exposure to others with viral syndromes, including sick siblings
      2. GI source (e.g. acute gastroenteritis). Often associated with diarrhea. Diarrhea is a symptom that usually exonerates shunt infection
      3. otitis media (check tympanic membranes)
      4. tonsillitis/pharyngitis
      5. appendicitis (peritoneal inflammation may impede VP shunt outflow)
      6. URI
      7. UTI
      8. pneumonia
   B. physical exam to R/O meningismus (stiff neck, photophobia…)
2. serum WBC count with differential
3. shunt tap: should be done in cases of suspected shunt infection. Shave and prep carefully to avoid introducing infection. GNB requires different therapy and has higher morbidity than staph, thus it is desirable to identify these rare patients: > 90% of these had positive Gram-stained CSF smear (only a few Gram-positive infections have positive results). GNB have higher protein and lower glucose, and neutrophils predominate in differential (unpublished data[12])
4. CT: usually not helpful for diagnosing infection. Ependymal enhancement when it occurs is diagnostic of **ventriculitis**. CT may demonstrate shunt

malfunction
5. abdominal U/S or CT: abdominal pseudocyst is suggestive of infection
6. ✖ LP: usually NOT recommended. May be hazardous in obstructive hydrocephalus **(HCP)** with a nonfunctioning shunt. Often does not yield the pathogen

TREATMENT

Antibiotics alone (without removal of shunt hardware)

Although eradication of shunt infections without removal of hardware has been reported[21 (p 595-7), 22], this has a lower success rate than with shunt removal[23], may require protracted treatment (up to 45 days in some), risks problems associated with draining infected CSF into the peritoneum (reduced CSF absorption, abdominal signs/symptoms including tenderness to full-blown peritonitis[21 (p 235)]) or vascular system (shunt nephritis (*see page 346*), sepsis…), and often requires at least partial shunt revision at some point in most cases. Treatment with antibiotics without shunt removal is therefore recommended only in cases where the patient: is terminally ill, is a poor anesthetic risk, or has slit ventricles that might be difficult to catheterize.

Removal of shunt hardware

In most instances, during the initial treatment with antibiotics the shunt is either externalized (i.e. tubing is diverted at some point distal to the ventricular catheter and connected to a closed drainage system), or sometimes the entire shunt may be removed. In the latter case, some means of CSF drainage must be provided in shunt dependent cases; either by insertion of an external ventricular drain **(EVD)**, or by intermittent ventricular taps or LPs (with communicating HCP). EVD allows easy monitoring of CSF flow, control of ICP, and repeated sampling for WBC determinations and cultures. In symptomatic patients or those with a positive CSF culture[24], any hardware removed should be cultured as only ≈ 8% are sterile in shunt infections. Skin organisms are fastidious and may take several days to grow.

If there is an abdominal pseudocyst, the fluid should be drained through the perito-neal catheter before removing it.

Empiric antibiotics

1. IV vancomycin used initially (penetration into CSF results in concentrations 18% that of serum).
2. PO rifampin may be added for increased coverage (10 mg/kg/day PO q 12 hrs)
3. when cultures return, change vancomycin to IV nafcillin unless patient is PCN allergic or cultures show MRSA (good penetration of inflamed meninges, lower toxicity than methicillin). If bactericidal activity is < 1:8, again consider adding rifampin
4. intraventricular injection of preservative-free antibiotics may be used in addition to IV therapy, clamp EVD x 30 minutes after injection

Treatment for specific organisms

Positive cultures from shunt hardware removed at the time of shunt revision in the absence of clinical symptoms or a positive CSF culture may be due to contamination and do not require treatment[24].

1. *S. aureus* and *S. epidermidis*
   A. if sensitive (MIC ≤ 1.0 μg/ml): IT gent + (IV nafcillin, or cefazolin, or cephalothin, or cephapirin)
   B. if resistant to nafcillin (i.e. MRSA), cephalothin, or cephapirin: PO rifampin + PO trimethoprim + IV & IT vancomycin
2. Enterococcus: IV/IT ampicillin + IT gent (if intravascular shunt: add IV gent)
3. other streptococci: either antistreptococcal or above enterococcal regimen
4. aerobic GNR: base on susceptibilities; both beta-lactam & APAG IV & IT indicated
5. *Serratia marcescens*: a rare cause of VP shunt infection[25] but the high morbidity may warrant aggressive antibiotic (IV + IT) and surgical therapy
6. *Corynebacterium spp.* & *Proprionibacterium spp.* (diphtheroids)
   A. if PCN sensitive: use enterococcal regimen above
   B. if PCN resistant: IV + IT vancomycin
7. *Candida spp.*: *see* page 346 for protocol, *see* page 345 for drugs

Intrathecal (IT) therapy

Yogev[12] cautions against high levels (caused neurologic effects in rabbits), he suggests striving for CSF concentrations comparable to peak blood values (e.g. 10-12 μg/ml for gent, or 25-30 μg/ml for amikacin).

Subsequent management

Once the CSF is sterile **x** 3 days, convert the EVD to a shunt (if an EVD was not used, it is still recommended that the shunt be replace with new hardware). Continue antibiotics an additional **10-14** days.

MANAGING VENTRICULOPERITONEAL SHUNTS IN PATIENTS WITH PERITONITIS

Peritonitis may occur as a result of:

1. perforation of a viscus (sometimes as a result of penetration by the peritoneal catheter tip[26], more common with obsolete Raimondi wire-reinforced tubing)
2. spontaneous bacterial peritonitis **(SBP)**: absence of an identifiable intraabdominal source. Most commonly diagnosed in patients with cirrhotic ascites[27]
3. or as a result of seeding through a VP shunt in a patient with a shunt infection: predominantly gram-positive, cutaneous organisms[28]

Concerns following en episode of peritonitis in a patient with VP shunt:

1. ascending infection into the CNS: uncommon, especially in the acute setting while on appropriate antibiotics with shunts containing a 1-way valve (as most do). CSF grows predominantly mixed, gram-negative intestinal flora[28]
2. contamination of the distal shunt: prevents permanent eradication of infection (appendicitis in the absence of peritonitis does not produce shunt infection[28])
3. shunt malfunction due to distal shunt obstruction: often as a result of walling off of the catheter tip, usually by omentum in reaction to the infection

Management recommendations following an episode of peritonitis (many viable options):

1. immediate appropriate treatment of peritonitis, usually managed by general surgeon (e.g. for ruptured appendix: appendectomy and appropriate antibiotics), with initial attempt to address shunt not being

mandatory

2. anecdotally, cases have been managed successfully by cleaning off the peritoneal catheter with bacitracin solution, and then wrapping the catheter in a bacitracin soaked lap sponge until the time to close the abdomen
3. if the peritonitis was diffuse or if the shunt catheter is believed to have been contaminated, an option is to externalize the distal catheter, preferably once the patient has stabilized from the peritonitis (afebrile, stable vital signs, normal WBC)
   A. externalization is done in a manner to avoid pulling contaminated catheter up towards hopefully sterile portions of the shunt. This can be accomplished by reopening the skin incision used for inserting the peritoneal catheter, and making a second incision over the shunt tubing, well above this entry point. The catheter is then divided at the upper incision. The catheter is grasped at the lower incision and is pulled, extracting both ends (the peritoneal end and the end just cut). The remaining catheter coming from above is connected to an external drainage system
   B. CSF cultures are monitored daily
   C. if 3 consecutive cultures are negative, a new distal catheter may be implanted
   D. if cultures continuously grow organisms, then the shunt may be contaminated and should then be replaced with an entirely new shunt system
   E. when it is time to replace the shunt, some authors[29, 30] recommend using an alternative site other than the peritoneum, but this is not mandatory[28]

16.4. Wound infections

16.4.1. Laminectomy wound infection

Occurs in 0.9-5% of cases[31]. May range from superficial to severe dehiscent wound infection. The risk is increased with age, long term steroid use, obesity, and possibly DM. Intraoperative mild hypothermia (as commonly occurs in the operating room) may also increase the risk of wound infection (as demonstrated

with colorectal resection[32]). Most are caused by *S. aureus*.

Management

1. culture the wound and/or any purulent drainage
2. start the patient empirically on vancomycin plus a third generation cephalosporin (e.g. ceftazidime)
3. modify antibiotics appropriately when culture and sensitivity results available
4. debride wound of all necrotic and devascularized tissue and any visible suture material (foreign bodies). Superficial wounds may be debrided in the office or treatment room, deep infections must be done in OR
5. shallow defects may be allowed to heal by secondary intention, and the following is one possible regimen
   A. pack the wound defect with 1/4” Iodophor® gauze
   B. dressing changes at least BID (for hospitalized patients, change q 8 hrs), remove and trim ≈ 0.5-1” of packing with each dressing change
      1. while wound is purulent, utilize 1/2 strength Betadine® wet to dry dressings
      2. when purulence subsides, switch to normal saline wet to dry
   C. antibiotics, may be useful as an adjunct to wound treatment initially, switch to oral antibiotics as early as possible, a duration of 10-14 days total is probably adequate if local wound care is being done
6. some prefer to close wound by primary intention[33], it is critical that there be no tension on the wound for healing to occur. Some close over an irrigation system or antibiotic beads. Retention sutures may be helpful[34]
7. with large defects or when bone and/or dura becomes exposed, the use of a muscle flap (often performed by a plastic surgeon) is probably required[31]
8. CSF leakage requires exploration in the OR with watertight dural closure to prevent meningitis

16.4.2. Craniotomy infection

Also, *see page 343* under meningitis, post-neurosurgical procedure.

C-reactive protein

Following uncomplicated craniotomy for microsurgery for brain tumors, C-

reactive protein (CRP) peaked on post-op day **(POD)** 2 with a mean value of 32 ± 38 mg/l[35]. Values declined from POD 3 through 5, reaching a mean of 6.7 ± 11 on POD 5. These values may be lower than with most post-op infections.

16.5. Osteomyelitis of the skull

The skull is normally very resistant to osteomyelitis, and hematogenous infection is rare. Most infections are due to contiguous spread (usually from an infected air sinus, occasionally from scalp abscess) or to penetrating trauma (including surgery and fetal scalp monitors[36]). With longstanding infection, edema and swelling in the area may become visible (usually over the forehead, but also may occur over the mastoids), and is called "**Pott puffy tumor**".

Staphylococcus is the most common organism, with *S. aureus* predominating, followed by *S. epidermidis*. In neonates, *E. coli* may be the infecting organism.

Imaging findings may include: bony resorption, periosteal reaction, contrast enhancement.

Treatment

Antibiotics alone are rarely curative. Treatment is usually surgical debridement of infected skull, biting off infected bone with rongeurs until a normal snapping sound replaces the more muted sound made by rongeuring infected bone. In the case of an infected craniotomy bone flap, the flap usually must be removed and the edges of the skull rongeured back to healthy bone. Closure of the scalp without cranioplasty is performed.

Surgery is followed by at least 6-12 weeks of antibiotics[37], usually IV for the first 1-2 weeks, then orally for the remainder. Until MRSA is ruled out, vancomycin + a 3rd generation cephalosporin are used. Once MRSA is ruled out, vancomycin may be changed to a penicillinase resistant synthetic penicillin (e.g. nafcillin). Most treatment failures occurred in patients treated with < 4 weeks of antibiotics following surgery.

Cranioplasty may be performed ≈ 6 mos post-op if there are no signs of infection,

16.6. Cerebral abscess

Key concepts:

- may arise from hematogenous spread, contiguous spread, or direct trauma
- risk factors: pulmonary abscess or AV fistulas, congenital cyanotic heart disease, immune compromise, chronic sinusitis/otitis, dental procedures
- symptoms are similar to any other mass lesions but tend to progress rapidly
- peripheral WBC may be normal or slightly ↑, CRP usually ↑
- organisms: Streptococcus is most common, up to 60% are polymicrobial
- imaging: usually round with thin enhancing ring on CT or MRI. T2WI → high signal lesion with thin rim of low intensity surrounded by hi signal (edema). Unlike with tumor, DWI often shows core of restricted diffusion (not reliable)
- treatment: IV antibiotics, needle drainage for some, excision infrequently (for fungal and resistant abscess)

Epidemiology

Approximately 1500-2500 cases per year in the U.S. Incidence is higher in developing countries. Male:female ratio is 1.5-3:1.

Risk factors

Risk factors include: pulmonary abnormalities (infection, AV-fistulas…, *see below*), congenital cyanotic heart disease (*see below*), bacterial endocarditis, penetrating head trauma (*see below*), chronic sinusitis or otitis media, and AIDS.

Vectors

Prior to 1980, the most common source of cerebral abscess was from contiguous spread. Now, hematogenous dissemination is the most common vector. In 10-60% no source can be identified[38].

Hematogenous spread

Abscesses arising by this means are multiple in 10-50% of cases[39]. No source can be found in up to 25% of cases. The chest is the most common origin:

- in adults: lung abscess (the most common), bronchiectasis and empyema
- in children: **congenital cyanotic heart disease (CCHD)** (estimated risk of abscess is 4-7%), especially tetralogy of Fallot. The increased Hct and low

PO_2 provides an hypoxic environment suitable for abscess proliferation. Those with rightto-left (veno-atrial) shunts additionally lose the filtering effects of the lungs (the brain seems to be a preferential target for these infections over other organs). Streptococcal oral flora is frequent, and may follow dental procedures. Coexisting coagulation defects often further complicate management[40]

- pulmonary arteriovenous fistulas: ≈ 50% of these patients have **Osler-Weber-Rendu syndrome** (AKA hereditary hemorrhagic telangiectasia), and in up to 5% of these patients a cerebral abscess will eventually develop
- bacterial endocarditis: only rarely gives rise to brain abscess[41]. More likely to be associated with acute endocarditis than with subacute form
- dental abscess
- GI infections: pelvic infections may gain access to the brain via Batson's plexus

In patients with septic embolization, the risk of cerebral abscess formation is elevated in areas of previous infarction or ischemia[42].

Contiguous spread

1. from purulent sinusitis: spreads by local osteomyelitis or by phlebitis of emissary veins. Virtually always singular. Rare in infants because they lack aerated para-nasal and mastoid air cells. This route has become less common due to improved treatment of sinus disease
   A. middle-ear and mastoid air sinus infections → temporal lobe and cerebellar abscess. The risk of developing a cerebral abscess in an adult with active chronic otitis media is ≈ 1/10,000 per year[43] (this risk appears low, but in a 30 year-old with active chronic otitis media the lifetime risk becomes ≈ 1 in 200)
   B. ethmoidal and frontal sinusitis → frontal lobe abscess
   C. sphenoid sinusitis: the least common location for sinusitis, but with a high incidence of intracranial complications due to venous extension to the adjacent cavernous sinus → temporal lobe
2. odontogenic → frontal lobe. Rare. Associated with a dental procedure in the past 4 weeks in most cases[44]. May also spread hematogenously

Following penetrating cranial trauma or neurosurgical procedure

Post-neurosurgical: especially with traversal of an air sinus. The risk of

abscess formation following civilian gunshot wounds to the brain is probably very low with the use of prophylactic antibiotics, except in cases with CSF leak not repaired surgically following traversal of an air sinus. An abscess following penetrating trauma cannot be treated by simple aspiration as with other abscesses, open surgical debridement to remove foreign matter and devitalized tissue is required. Abscess has been reported following use of intracranial pressure monitors and halo traction[45].

PATHOGENS

1. cultures from cerebral abscesses are sterile in up to 25% of cases
2. organisms recovered varies with the primary source of infection
3. in general: Streptococcus is the most frequent organism, 33-50% are anaerobic or microaerophilic. Multiple organisms may be cultured to varying degrees, usually in only 10-30% of cases, but can approach 60%[38], and usually includes anaerobes (Bacteroides sp. common)
4. when secondary to fronto-ethmoidal sinusitis: *Strep. milleri* and *Strep. anginosus* may be seen
5. from otitis media, mastoiditis, or lung abscess: usually multiple organisms, including anaerobic strep., Bacteroides, Enterobacteriaceae (Proteus)
6. post traumatic: usually due to *S. aureus* or Enterobacteriaceae
7. odontogenic (dental) source: may be associated with Actinomyces
8. following neurosurgical procedures: *Staph. epidermidis* and *aureus* may be seen
9. immunocompromised hosts including transplant patients (both bone marrow and solid organ) and AIDS: fungal infections are more common than otherwise would be seen. Organisms include:
   A. *Toxoplasma gondii*: *see page 365* and *page 367*
   B. *Nocardia asteroides*: *see page 356*
   C. *Candida albicans*
   D. *Listeria monocytogenes*
   E. mycobacterium
   F. *Aspergillus fumigatus* often from a primary pulmonary infection
10. infants: Gram negatives are common because IgM antibodies don’t cross placenta

PRESENTATION

Symptoms: none are specific for abscess, and many are due to edema

surrounding the lesion. Most are due to increased ICP (H/A, N/V, lethargy). Hemiparesis and seizures develop in 30-50% of cases. Papilledema is rare before 2 yrs of age. Symptoms tend to progress more rapidly than with neoplasms.

Newborns: patent sutures and poor ability of infant brain to ward off infection → cranial enlargement. Common: seizures, meningitis, irritability, increasing OFC, and failure to thrive. Some authors say most newborns with abscess are afebrile. Tend not to do well.

EVALUATION

BLOODWORK

Peripheral WBC: may be normal or only mildly elevated in 60-70% of cases (usually > 10,000).

Blood cultures: should be obtained when abscess is suspected, usually negative.

ESR: may be normal (especially in congenital cyanotic heart disease where polycythemia lowers the ESR).

C-reactive protein **(CRP)**: infection anywhere in body (including brain abscess and dental abscess) can raise the CRP level. May also be elevated in noninfectious inflammatory conditions and brain tumor. Sensitivity for abscess is ≈ 90%, specificity is ≈ 77%[46]. For normal values *see page 387*.

LUMBAR PUNCTURE (LP)

The role of LP is very dubious in abscess. Although LP is abnormal in > 90%, there is no characteristic finding diagnostic of abscess. The OP is usually increased, and the WBC count and protein may be elevated. The offending organism can rarely be identified from CSF obtained by LP (unless abscess ruptures into ventricles) with positive cultures in ≈ 6-22%[47]. There is a risk of transtentorial herniation, especially with large lesions (*see page 203* for discussion).

Σ ✖ Due to the risk involved and the low yield of useful information, avoid LP if not already done.

BRAIN IMAGING

CT: ring enhancing. Sensitivity ≈ 100%. For CT staging of abscess *see below*.

MRI: *see Table 16-2* for findings. Enhanced T1WI → thin-walled ring enhancement surrounding low intensity central region (*Figure 35-1*, page 1214).

Fluid-fluid levels may be seen. Occasionally gas producing organisms may cause pneumocephalus.

Diffusion MRI: DWI → bright, ADC → dark (restricted diffusion suggesting viscous fluid)[48] (see *Figure 35-1*, page 1214). Unlike most tumors which are dark on DWI (see *Figure 35-2*, page 1214). More reliable with pyogenic abscess, less reliable e.g. with fungal[49] or TB abscess).

MR-spectroscopy: amino acids and acetate or lactate are diagnostic for abscess.

Leukocyte scan with ^{99m}Tc-HMPAO: patient's own WBCs are tagged and reinjected. Close to 100% sensitivity and specificity (sensitivity will be reduced if patient is treated with steroids within 48 hrs prior to the scan)[46].

ADDITIONAL EVALUATION

CXR and chest CT (if indicated) to look for pulmonary source.

Cardiac echo (Doppler and/or echo with agitated saline injection (bubble study)): for suspected hematogenous spread, to look for patent foramen ovale or cardiac vegetations.

STAGING OF CEREBRAL ABSCESS

Table 16-1 shows the four well recognized histologic stages of cerebral abscess, and correlates this with the resistance to insertion of an aspirating needle at the time of surgery. It takes at least 2 weeks to progress through this maturation process, and steroids tend to prolong it.

Table 16-1 Histologic staging of cerebral abscess

Stage	**Histologic characteristics** (days shown are general estimates)	**Resistance to aspirating needle**
1	**early cerebritis**: (days 1-3) early infection & inflammation, poorly demarcated from surrounding brain, toxic changes in neurons, perivascular infiltrates	intermediate resistance
2	**late cerebritis**: (days 4-9) reticular matrix (collagen precursor) & developing necrotic center	no resistance
3	**early capsule**: (days 10-13) neovascularity, necrotic center, reticular network surrounds (less well developed along side facing ventricles)	no resistance
4	**late capsule**: (> day 14) collagen capsule*, necrotic center, gliosis around capsule	firm resistance, "pop" on entering

* abscess is ≈ the only process in the brain that leaves a collagen scar, all other scars are glial scars

CT staging

Late cerebritis (stage 2) has similar features to early capsule (stage 3) on routine contrast and non-contrast CT. There is some therapeutic importance in differentiating these two stages; the following aids in distinguishing[50]:

- cerebritis: tends to be more ill-defined
  A. ring-enhancement: usually appears by late cerebritis stage, usually thick
  B. further diffusion of contrast into central lumen, and/or lack of decay of enhancement on delayed scan 30-60 min after contrast infusion
- capsule:
  A. faint rim present on pre-contrast CT (necrotic center with edematous sur-rounding brain cause collagen capsule to be seen)
  B. thin ring enhancement AND delayed scans → decay of enhancement

NB: Thin ring enhancement but lack of delayed decay correlates better with cerebritis

NB: Steroids reduce degree of contrast enhancement (especially in cerebritis)

MRI staging

Table 16-2 shows MRI findings in cerebral abscess. In the cerebritis stage, the margins are ill defined.

Table 16-2 MRI findings with cerebral abscess

Stage	T1WI	T2WI
cerebritis	hypointense	hi signal
capsular	lesion center → low signal, capsule → mildly hyperintense, perilesional edema → low signal	center → iso- or hyperintense, capsule → dark (collagen), perilesional edema → hi signal

TREATMENT

"There is no single best method for treating a brain abscess." Treatment usually involves surgical drainage or excision, correction of the primary source, and long-term use of antibiotics (often IV **x** 6-8 weeks followed by oral route **x** 4-8 weeks).

SURGICAL VS. PURE MEDICAL MANAGEMENT

In a patient with suspected cerebral abscess, tissue should be obtained in almost every case to confirm diagnosis and to identify pathogens (preferably

before antibiotics).

Medical treatment

In general, surgical drainage or excision is employed in the treatment. Purely medical treatment of early abscess (cerebritis stage)[51], is controversial. NB: pathogens were cultured from well encapsulated abscesses despite adequate levels of appropriate antibiotics in 6 patients who failed medical therapy[52]. Failure may be due to poor blood supply and acidic conditions within the abscess (which may inactivate antibiotics in spite of concentrations exceeding the MIC).

Medical therapy alone is more successful if:

1. treatment begun in cerebritis stage (before complete encapsulation), even though many of these lesions subsequently go on to become encapsulated
2. small lesions: diameter of abscesses successfully treated with antibiotics alone were 0.8-2.5 cm (1.7 mean). Those that failed were 2-6 cm (4.2 mean). ★ **3 cm** is suggested as a cutoff[53], above this surgery should be included
3. duration of symptoms ≤ 2 wks (correlates with cerebritis stage)
4. patients show definite clinical improvement within the first week

Medical management alone considered if:

1. poor surgical candidate (NB: with local anesthesia, stereotactic biopsy can be done in almost any patient with normal blood clotting)
2. multiple abscesses, especially if small
3. abscess in poorly accessible location: e.g. brain stem[54]
4. concomitant meningitis/ependymitis

Surgical treatment

Indications for initial surgical treatment include:

1. significant mass effect exerted by lesion (on CT or MRI)
2. difficulty in diagnosis (especially in adults)
3. proximity to ventricle: indicates likelihood of intraventricular rupture which is associated with poor outcome[40, 55]
4. evidence of significantly increased intracranial pressure
5. poor neurologic condition (patients responds only to pain, or does not even response to pain)
6. traumatic abscess associated with foreign material

7. fungal abscess
8. multiloculated abscess
9. follow-up CT/MRI scans cannot be obtained every 1-2 weeks

Surgical intervention in patient being treated medically:

Intervention if neurological deterioration, progression of abscess towards ventricles, or after 2 wks if the abscess is enlarged. Also considered if no decrease in size by 4 wks.

SPECIFIC MANAGEMENT

- obtain blood cultures (rarely helpful)
- initiate antibiotic therapy (preferably after biopsy specimen obtained), regardless of which mode of treatment (medical vs. surgical) is chosen (*see below*)
- LP: avoid in most cases of cerebral abscess (*see page 352*)
- anticonvulsants: indicated for seizures, prophylactic use is optional
- steroids: controversial. Reduces edema, but may impede therapy (*see below*)

ANTIBIOTICS

1. initial antibiotics of choice (when pathogen unknown, and especially if *S. aureus* suspected), make appropriate changes as sensitivities become available. If there is no history of trauma or neurosurgical procedure, then the risk of MRSA is low:
   - vancomycin: covers MRSA. Adult: 1 gm IV q 12 hr. Peds: 15 mg/kg q 8 hr. Check peak & trough levels and adjust dose accordingly

   PLUS
   - a 3rd generation cephalosporin (e.g. cefotaxime (Claforan®))

   PLUS
   - one of the following
     - ◆ metronidazole (Flagyl®). Adult: 30 mg/kg/d total usually IV (divided q 12 hrs or q 6 hrs, not to exceed 4 gm/d). Peds: 10 mg/kg IV q 8 hrs

     OR
     - ◆ chloramphenicol. Adult: 1 gm IV q 6 hr. Peds: 15-25 mg/kg IV q 6 hr OR
     - ◆ for post-traumatic abscess, use PO rifampin 9 mg/kg/d as 1 dose
2. if culture shows no staph (as is usual in non-traumatic abscess), change

nafcillin to PCN G (high dose): adult: 5 M units IV q 6 hr; peds: 50,000-75,000 units/kg IV q 6 hr
3. if culture shows only strep, may use PCN G (high dose) alone
4. if cultures show staph that is not MRSA and the patient is not allergic to penicillin or nafcillin, substitute nafcillin for the vancomycin. Adult: 2 gm IV q 4 hrs. Peds: 25 mg/kg IV q 6 hrs
5. *Cryptococcus neoformans, Aspergillus sp., Candida sp.*:
   A. amphotericin B: 0.5-1 mg/kg/day. Abelcet® (amphotericin B lipid complex) 5 mg/kg/d should be used when renal function is compromised
   B. or liposomal amphotericin B: 3 mg/kg/day, increase to 15 mg/kg/d
6. in AIDS patients: *Toxoplasma gondii* is a common pathogen, and initial empiric treatment with sulfadiazine + pyrimethamine is often used (*see page 366*)

Duration of antibiotics

IV antibiotics for 6-8 wks (most commonly 6), may then D/C even if the CT abnormalities persist (neovascularity remains). NB: CT improvement may lag behind clinical improvement. Duration of treatment may be reduced if abscess and capsule entirely excised surgically. Oral antibiotics may be used following IV course. 5-20% of abscesses recur within 6 weeks of discontinuing antibiotics.

Steroids

Reduces edema, Decreases likelihood of fibrous encapsulation of abscess. May reduce penetration of antibiotics into abscess 53. Immune suppression may also be deleterious. ★ Reserved for patients with clinical and imaging evidence of deterioration from marked mass effect, and duration of therapy should be minimized.

Follow-up imaging

If therapy is successful, imaging should show decrease in:
1. degree of ring enhancement
2. edema
3. mass effect
4. size of lesion: takes 1 to 4 wks (2.5 mean). 95% of lesions that will resolve with antibiotics alone decrease in size by 1 month

SURGICAL TREATMENT

Current options[56]:

1. needle aspiration: the mainstay of surgical treatment. Especially well-suited for multiple or deep lesions (*see below*)
2. surgical excision: prevents recidivism. Shortens length of time on antibiotics. Recommended in traumatic abscess to debride foreign material (especially bone), and in fungal abscess because of relative antibiotic resistance (*see below*)
3. external drainage: controversial. Not frequently used
4. instillation of antibiotics directly into the abscess: has not been extremely efficacious, although it may be used as for refractory *Aspergillus* abscesses

NEEDLE ASPIRATION

If necessary, may be performed under local anesthesia. May be combined with irrigation with antibiotics or normal saline. Needs to be repeated in up to 70% of cases. May be the only surgical intervention required, but sometimes must be followed with excision (especially with multiloculated abscess). Stereotactic drainage may be ideal for deep lesions[57].

Performed through a trajectory chosen to:

1. minimize the path length through the brain
2. avoid traversing the ventricles or vital neural or vascular structures
3. avoid traversing infected structures outside the intracranial compartment (infected bone, paranasal sinuses, and scalp wounds)
4. in cases of multiples abscesses, target[39]:
    A. the largest lesion or the one causing the most symptoms
    B. once the diagnosis of abscess is confirmed
        1. any lesion ≥ 2.5 cm diameter
        2. lesions causing significant mass effect
        3. enlarging lesions

Cultures

Send aspirated material for the following:

1. stains
    A. Gram stain
    B. acid-fast stain (AFB stain) for Mycobacterium
    C. modified acid-fast stain (for Nocardia, *see below*) looking for

branching acid fast bacillus

D. special fungal stains (e.g., methenamine silver, mucicarmine)

2. culture

A. routine cultures: aerobic and anaerobic

B. fungal culture: this is not only helpful for identifying fungal infections, but since these cultures are kept for longer period and any growth that occurs will be further characterized, fastidious or indolent bacterial organisms may sometimes be identified

C. TB culture

EXCISION

Can only be performed during the "chronic" phase (late capsule stage). Abscess is removed as any well encapsulated tumor. The length of time on antibiotics can be shortened to ≈ 3 days in some cases following total excision of an accessible, mature abscess (e.g. located in pole of brain). Recommended for abscesses associated with foreign body and most *Nocardia* abscesses (*see below*). May also be needed necessary for: fungal abscess, multiloculated or resistant lesions.

Table 16-3 Outcomes with cerebral abscess

mortality (CT era data)[39, 58]	0-10%
neurologic disability	45%
late focal or generalized seizures	27%
hemiparesis	29%

OUTCOME

In the pre-CT era, mortality ranged form 40-60%. With improvement in antibiotics, surgery, and the improved ability to diagnose and follow response with CT/MRI, mortality rate has been reduced to ≈ 10%, but morbidity remains high with permanent neurologic deficit or seizures in up to 50% of cases. Current outcomes are shown in *Table 16-3*. A worse prognosis is associated with poor neurologic function, intraventricular rupture of abscess, and almost 100% mortality with fungal abscesses in transplant recipients.

16.6.1. Some unusual organisms producing abscess

Nocardia

Nocardiosis is caused primarily by *Nocardia asteroides* (other Nocardia species such as *N. brasiliensis* are less common), a soil-born aerobic actinomycete (a bacteria, not a fungus) that is usually inoculated through the respiratory tract and produces a localized or disseminated infection. Hematogenous spread frequently results in cutaneous lesions and CNS involvement. Nocardia is responsible for 2% of all brain abscesses, the majority of these are *N. asteroides*.

Nocardiosis occurs primarily in patients with chronic debilitating illnesses including:

1. neoplasms: leukemia, lymphoma…
2. conditions requiring long-term corticosteroid treatment
3. Cushing's disease
4. Paget's disease of bone
5. AIDS
6. renal or cardiac organ transplant recipients

The diagnosis is suspected in high-risk patients presenting with soft-tissue abscesses and CNS lesions. CNS involvement occurs in about one-third and includes:

1. cerebral abscess: often multiloculated
2. meningitis
3. ventriculitis in patients with CSF shunt[59]
4. epidural spinal cord compression from vertebral osteomyelitis[60]

Diagnosis

Brain biopsy may not be needed in high-risk patients with confirmed nocardia infection in other sites[59], except possibly in AIDS patients where the risk of multiple organism infections or infection plus tumor (particularly lymphoma) is considerable.

Treatment

As for most abscesses, very small ones may be treated medically, lesions up to about 3 cm may undergo needle aspiration first, and larger lesions or those that grow despite medical therapy may require excision followed by antibiotics.

Medical treatment: Primary choice is trimethoprim-sulfamethoxazole **(TMP-SMZ)**.

Rx: start with 15 mg/kg/d of TMP & 75 mg/kg/d of SMZ IV or PO divided in 2-4 doses. After 3-4 weeks, decrease to 10 mg/kg/d TMP in 2-4 doses PO. Check serum levels.

Alternatives: imipenem + amikacin. Also possibly effective: linezolid[61].

Duration: because of risks of relapse or hematogenous spread, treatment is recommended for 3 months in immunocompetent hosts and 6 months for immunocompromised.

16.7. Subdural empyema

Referred to as subdural abscess prior to 194362. Subdural empyema **(SDE)** is a suppurative infection that forms in the subdural space, which has no anatomic barrier to spread[63] Antibiotic penetration into this space is poor. Distinguished from abscess which forms within brain substance, surrounded by tissue reaction with fibrin and collagen capsule formation. Hence, SDE tends to be more emergent.

SDE may be complicated by cerebral abscess (seen in 20-25% of imaging studies), cortical venous thrombosis with risk of venous infarction, or localized cerebritis.

Epidemiology

Less common than cerebral abscess (ratio of abscess:empyema is ≈ 5:1). Found in 32 cases in 10,000 autopsies. Male:female ratio is 3:1.

Location: 70-80% are over the convexity, 10-20% are parafalcine.

Etiologies

See *Table 16-4*. Most often occurs as a result of direct extension of local infection (rarely following septicemia). Spread of the infection to the intracranial compartment may occur through the valveless diploic veins, often with associated thrombophlebitis[66].

Chronic otitis media was the leading cause of SDE in the preantibiotic era, but has now been surpassed by paranasal sinus disease especially with frontal sinus involvement[64] (may also follow mastoid sinusitis). SDE is a rare but sometimes fatal complication of cranial traction devices[64, 67]. Infection of

preexisting subdural hematomas (both treated and un-treated, in infants and adults) have been reported[64].

Trauma includes compound skull fractures and penetrating injuries. Other etiologies include: osteomyelitis, pneumonia, unrelated infection in diabetics.

Table 16-4 Etiologies of SDE

Location	%
paranasal sinusitis (especially frontal)*	67-75
otitis (usually chronic otitis media)†	14
post surgical (neuro or ENT)	4
trauma	3
meningitis (more common in peds[65])	2
congenital heart disease	2
misc. (including pulmonary suppuration)	4
undetermined	3

* more common in adults

† no cases from otitis in a recent series[64]

Presentation

Neurologic findings are shown in *Table 16-5*. Symptoms are due to mass effect, inflammatory involvement of the brain and meninges, and thrombophlebitis of cerebral veins and/or venous sinuses. SDE should be suspected in the presence of meningismus + unilateral hemisphere dysfunction. Marked tenderness to percussion or pressure over affected air sinuses is common[63]. Forehead or eye swelling (from emissary vein thrombosis) may occur.

Focal neurologic deficit and/or seizures usually occur late.

Table 16-5 Findings on presentation with SDE*

Finding	%
fever	95
H/A	86
meningismus (nuchal rigidity…)	83
hemiparesis	80

altered mental status	76
seizures	44
sinus tenderness, swelling or inflammation	42
nausea and/or vomiting	27
homonymous hemianopsia	18
speech difficulty	17
papilledema	9

* from a review of multiple articles[64]

Evaluation

- **CT**: IV contrast is usually helpful. CT may miss some cases (related to early generation scanners, failure to give IV contrast, poor scan quality…). If normal, repeat the CT at a later time or do an MRI if clinical suspicion persists. Findings: hypodense (but denser than CSF) crescentic or lenticular extracerebral lesion with dense enhancement of medial membrane; inward displacement of gray-white interface; ventricular distortion and effacement of basal cisterns are common findings[68]
- **MRI**: low signal on T1WI, high signal on T2WI. Pial ependymal line: a non-specific MRI finding in CNS infection
- **LP**: ✖ potentially hazardous (risk of herniation). Organisms are usually present only in cases originating from meningitis. If no meningitis: moderate sterile pleocytosis (150-600 WBC/mm^3) with PMNs predominating; glucose normal; opening pressure is usually high[63]; protein is usually elevated (range: 75-150 mg/dl)

Table 16-6 Organisms in adult cases of SDE associated with sinusitis

aerobic streptococcus	30-50%
staphylococci	15-20%
microaerophilic and anaerobic strep	15-25%
aerobic Gram-negative rods	5-10%
other anaerobes	5-10%

Table 16-7 Organisms in SDE in childhood (age < 5 years)

Organisms are similar to meningitis for the same age group. Antibiotics choice is the same as for meningitis

ORGANISMS

The causative organism varies with the specific source of the infection. SDE associated with sinusitis is often caused by aerobic and anaerobic streptococci (*see Table 16-6*). Following trauma or neurosurgical procedures, staphylococci and Gram-negative species predominate. Sterile cultures occur in up to 40%. For SDE in peds, *see Table 16-7*.

TREATMENT

1. surgical drainage: indicated in most cases (nonsurgical management has been reported[69], but should only be considered with minimal neurologic involvement, limited extension and mass effect of SDE, and early favorable response to antibiotics) usually done relatively emergently

- early in the course, the pus tends to be more fluid and may be more amenable to burr hole drainage; later, loculations develop which may necessitate craniotomy
- there has been controversy over the optimal surgical treatment. Early studies indicated a better outcome with craniotomy. Recent studies show less difference
    A. critically ill patients with localized SDE may be candidates for burr-hole drainage (usually inadequate if loculations are present). Repeat procedures may be needed, and up to 20% will later require a craniotomy
    B. craniotomy: to debride and, if possible, drain. A wide craniotomy is often required because of septations. The dura appears white because of pus underneath. Open and wash out subdural space. Do not try to remove material adherent to cortex (may cause infarction)

2. antibiotics: similar to treatment for cerebral abscess
    - initially: a penicillin and a third-generation cephalosporin (e.g. cefotaxime)
    - metronidazole is added if there is a high suspicion of anaerobes
    - for post-op SDE: substitute vancomycin for PCN (switch vancomycin to a PCN if there is no staphylococcus)
    - modify antibiotics based on culture results
    - duration: usually 4-6 weeks

- anticonvulsants: usually used prophylactically, mandatory if seizures occur

OUTCOME

See *Table 16-8*. Neurologic deficits were present in 55% of patients at the time of discharge[64]. Age ≥ 60 years, obtundation or coma at presentation, and SDE related to surgery or trauma carry a worse prognosis[64]. Burr-hole drainage may be associated with a worse outcome than with craniotomy, but this may have been influenced by the poorer condition of these patients. Fatal cases may have associated venous infarction of the brain.

Table 16-8 Outcome with SDE

persistent seizures	34%
residual hemiparesis	17%
mortality	10-20%

16.8. Viral encephalitis

Encephalitides that come to the attention of the neurosurgeon usually cause imaging findings that may mimic mass lesions. Biopsy is helpful in some instances, and shunting for hydrocephalus may occasionally be needed. Those covered in this book:

1. herpes simplex encephalitis: *see below*
2. multifocal herpes varicella-zoster virus leukoencephalitis: *see page 360*
3. progressive multifocal leukoencephalopathy **(PML)**: *see page 364*

16.8.1. Herpes simplex encephalitis

Key concepts:

- a hemorrhagic viral encephalitis with a predilection for temporal lobes
- definitive diagnosis requires brain biopsy
- optimal treatment: early administration of IV acyclovir

Herpes simplex encephalitis **(HSE)** AKA multifocal necrotizing encephalomyelitis, is caused by the herpes simplex virus **(HSV)** type I. It produces an acute, often (but not always) hemorrhagic, necrotizing encephalitis with edema. There is a predilection for the temporal and orbitofrontal lobes and limbic system.

EPIDEMIOLOGY[70]

Estimated incidence of HSE: 1 in 750,000 to 1 million persons/yr. Equally distributed between male and females, in all races, in all ages (over 33% of cases occur in children 6 mos to 18 yrs), throughout the year.

PRESENTATION

Patients are often confused and disoriented at onset, and progress to coma within days. Adult presentations are shown in *Table 16-9*, and for pediatrics in *Table 16-10*. Other symptoms include headache.

Table 16-9 Adult presentation

altered consciousness	97%
fever	90%
seizures (usually focal onset)	67%
personality changes	71%
hemiparesis	33%

Table 16-10 Presentation in age < 10 yrs

irritability	altered mentation
malaise	seizure
disorientation	dysphasia
hemiparesis	fever
papilledema (except in age ≤ 2 yrs)	

DIAGNOSTIC STUDIES

Diagnosis can often be made on the basis of history, CSF, and MRI. Treatment should be instituted rapidly without waiting for biopsy, before the onset of coma.

1. **CSF:** leukocytosis (mostly monos), RBCs 500-1000/mm^3, (NB: 3% have no pleocytosis), protein rises markedly as disease progresses. HSV antibodies may appear in the CSF but takes at least ≈ 14 days and is thus not useful for early diagnosis
2. **EEG:** periodic lateralizing epileptiform discharges **(PLEDs)** (triphasic high-voltage discharges every few seconds) usually from the temporal

lobe. EEG may vary rapidly over few days (unusual in conditions mimicking HSE)

3. **CT:** edema predominantly localized in temporal lobes (poorer prognosis once hemorrhagic lesions visible). In one review, 38% of initial CTs were normal[71] (many were on early generation CT scanners or were done within 3 days of onset). Hemorrhages were apparent in only 12% of the initially abnormal CTs
4. **MRI:** more sensitive than CT[72], demonstrates edema as high signal on T2WI, primarily within the temporal lobe, with some extension across sylvian fissure ("transsylvian sign")[71], especially suggestive of HSE if bilateral. Differentiate from MCA infarct (which may also span sylvian fissure) by typical arterial distribution of the latter. Enhancement doesn't occur until the 2nd week
5. **technetium brain scan:** process localized to temporal lobes
6. **brain biopsy:** false negatives may occur[73]
   A. **indications:** reserved for questionable cases. May not be necessary in patients with fever, encephalopathy, compatible CSF findings, focal neuro findings (focal seizure, hemiparesis, or cranial nerve palsy), and supporting evidence of at least one of the following: focal EEG, CT, MRI or technetium brain scan abnormality
   B. should be performed within ≤ 48 hrs of starting acyclovir (otherwise false negatives may occur)
   C. anterior inferior temporal lobe is preferred site
      1. the side chosen for biopsy is the one showing maximal involvement based on clinical information (e.g. localizing seizures), EEG and/or imaging studies[74]
      2. 10 **x** 10 **x** 5 mm deep specimen obtained from anterior portion of the inferior temporal gyrus with NO COAGULATION on specimen side (cut surface with #11 blade, then cauterize pial surface on <u>non</u>-specimen side)
      3. 2nd specimen obtained from beneath surface specimen with fenestrated pituitary biopsy forceps
   D. virus isolation is the most specific (100%) and sensitive (96-97%) test for HSE. Other findings (less accurate): perivascular cuffing, lymphocytic infiltration, hemorrhagic necrosis, neuronophagia, intranuclear inclusions (present in 50%)
   E. if electron microscopy (EM) or immunohistofluorescence is available,

70% may be diagnosed within ≈ 3 hrs of biopsy

F. biopsy tissue handling

1. avoid macerating specimens for histology
2. tissue for EM: placed in glutaraldehyde
3. tissue for permanent histology: placed in formalin
4. tissue for culture:
   a. handling: specimen is placed in sterile specimen container and sent directly to virology lab. If lab is closed, tissue may be:
      i. placed in regular refrigerator for up to 24 hrs
      ii. placed in –70° C freezer for indefinite time (virus remains viable for up to 5 yrs)
      iii. DO NOT place in regular freezer (destroys virus)
   b. cultures generally take at least 1 week to become positive
   c. cultures checked for 3 weeks before being declared negative

G. biopsy results: of 432 brain biopsies meeting the above criteria, 45% had HSE, 22% had identifiable but non HSE pathology (e.g. vascular disease, other viral infection, adrenal leukodystrophy, bacterial infection…), and 33% remained without a diagnosis[75]

TREATMENT

General supportive measures: to control elevated ICP from edema, includes: elevate HOB, mannitol, hyperventilation (dexamethasone unproven efficacy) (also see *Treatment measures for elevated ICP*, page 876). Phenytoin is used for seizure prophylaxis.

Antiviral medications

Ganciclovir is gaining favor over acyclovir.

acyclovir (Zovirax®) **DRUG INFO**

***Rx* Adult**: 30 mg/kg/day, in divided q 8 hr doses in minimum volume of 100 ml IV fluid over 1 hr (caution: this fluid load may be hazardous, especially since cerebral edema is already usually problematic) for 14-21 days (some relapses have been reported after only 10 days of treatment).

***Rx* Children** > 6 mos age: 500 mg/m^2 IV q 8 hrs **x** 10 days.

***Rx* Neonatal**: 10 mg/kg IV q 8 hrs for 10 days.

vidarabine (Vira-A®) **DRUG INFO**

Outcome

Six month mortality following treatment with acyclovir was influenced by:

- age (6% under age 30, 36% over age 30)
- Glasgow coma score **(GCS)** at time of treatment initiation (25% for GCS ≤ 10, 0% for GCS > 10)
- duration of disease before therapy (0% for initiating therapy within 4 days, 35% if after 4 days)

16.8.2. Multifocal varicella-zoster leukoencephalitis

Caused by the herpes varicella-zoster virus **(VZV)** which is responsible for varicella (chickenpox), herpes zoster **(HZ)** (shingles), and post-herpetic neuralgia (*see* *page 564*). VZV is a herpesvirus that is distinct from the *herpes simplex virus*.

Symptomatic zoster-related encephalitis occurs in < 5% of immunocompromised patients (including AIDS patients) with cutaneous zoster[76]. It typically follows cutaneous HZ by a short time (average: 9 days) although cases have been reported where many months have lapsed[77].

Manifestations include: altered level of consciousness, headache, photophobia, meningismus. Although focal neurologic deficits may occur, these are uncommon.

MRI may show multiple, discrete, round and oval lesions with minimal edema (best seen on T2WI) and minimal enhancement.

Unlike herpes simplex virus, VZV is difficult to isolate in culture. On brain biopsy, look for multiple discrete lesions within grey and white matter, with Cowdry type A intranuclear inclusion bodies in oligodendrocytes, astrocytes, and neurons, and a positive direct fluorescent antibody test directed against VZV.

There is a case report of VZV encephalitis treated with IV acyclovir[76].

16.9. Creutzfeldt-Jakob disease

Key concepts

- an invariably fatal encephalopathy characterized by rapidly progressive dementia, ataxia and myoclonus
- death usually occurs within 1 yr of onset of symptoms
- 3 forms: 1) transmissible (possibly via prions), 2) autosomal dominant inherited, 3) sporadic
- characteristic EEG finding: bilateral sharp wave (0.5-2 per second)
- pathology: status spongiosus without inflammatory response

Creutzfeldt-Jakob disease **(CJD)** is one of 4 known rare human diseases associated with transmissible spongiform encephalopathy agents, also called prions (proteinaceous infectious particles). Although sometimes also referred to as a "slow virus", these agents contain no nucleic acids and are also resistant to processes that inactivate conventional viruses (*see Table 16-12*). Prions do not provoke an immune response. The protease-resistant protein associated with disease is designated PrP^{res} or PrP^{Sc}, and is an isoform of a naturally occurring protease-sensitive protein designated PrP^{sen} or PrP^{C}.

Annual incidence of CJD: 0.5-1.5 per million population[78]. Over 200 people die of CJD in the U.S. each year. CJD occurs in 3 forms: transmissible, inherited and sporadic.

Acquired prion diseases: Natural route of infection is unknown and virulence appears low, with lack of significant dissemination by respiratory, enteric, or sexual contact. There is no increased incidence in spouses (only a single conjugal pair of cases has been verified), physicians or laboratory workers. There is no evidence of transplacental transmission. The only known cases of horizontal transmission of CJD have occurred iatrogenically (*see below*). Kuru has been transmitted via handling and ingestion of infected brains in ritualistic funereal cannibalism practiced among the Fore (pronounced: "foreay") linguistic group in the eastern highlands of Papua, New Guinea[79], a practice which was generally abandoned in the 1950's. Kuru is a subacute, uniformly fatal disease involving cerebellar degeneration (the word "kuru" means "to tremble" in the local language[80 (p 6)]).

Most noniatrogenically transmitted cases of CJD occur in patients > 50 yrs old, and is rare in age < 30. The incubation period can range from months to decades. The onset of symptoms following direct inoculation is usually faster (common range: 16-28 mos), but still may be much longer (up to 30 years with corneal transplant[81], and 4-21 yrs with hGH transmission).

Inherited CJD: 5-15% of cases of CJD occur in an autosomal dominant inheritance pattern with abnormalities in the amyloid gene[82] on chromosome 20 with a penetrance of 0.5683. Since familial CJD is dominantly inherited, analysis for the PrP gene is not indicated unless there is a history of dementia in a first degree relative.

Sporadic CJD: In ≈ 90% of cases of CJD, no infectious or familial source can be identified[82], and these cases are considered sporadic. 80% occur in persons 50-70 yrs old[78]. Sporadic cases show no abnormality in the PrP gene.

New variant CJD: Cases of atypical CJD are well-recognized. A new variant of CJD **(vCJD)** was identified in 10 cases of unusually young individuals (median age at death: 29 yrs) during 1994-95 in the United Kingdom[84], and has been strongly linked to the 1980s epidemic of bovine spongiform encephalopathy **(BSE)**, dubbed "mad cow" disease by the lay press. None of the vCJD patients had periodic spikes on EEG characteristic of classic CJD, the clinical course was atypical (having prominent psychiatric symptoms and early cerebellar ataxia, some-what similar to kuru), and brain plaques showed unusual features also reminiscent of amyloid plaques seen in kuru. A comparison of vCJD to sporadic CJD is shown in *Table 16-11*.

Table 16-11 Comparison of vCJD to sporadic CJD[78]

Characteristic	vCJD	sporadic
mean age at onset (yr)	29	60
mean duration of disease (mo)	14	5
most consistent and prominent early signs	psychiatric abnormalities, sensory symptoms	dementia, myoclonus
cerebellar signs (%)	100	40
periodic complexes on EEG (%)	0	94
pathological changes	diffuse amyloid plaques	sparse plaques in 5-10%

Iatrogenic transmission of CJD

Described only in cases of direct contact with infected organs, tissues or surgical instruments. Has been reported with: corneal transplants[81, 87], intracerebral EEG electrodes sterilized with 70% alcohol and formaldehyde

vapor after use on a CJD patient[88], operations in neurosurgical O.R.s after procedures on CJD patients, in recipients of pituitary-derived[A] human growth hormone **(hGH)**[89], and dural graft with cadaveric dura mater (Lyodura®). Recommended sterilization procedures for suspected CJD tissues and contaminated materials appear in *Table 16-12*.

A. there is no longer a risk of CJD with growth hormone in the U.S. since distribution of pituitary derived hGH was halted in 1985 and current hGH is obtained from recombinant DNA technology

Pathology

The typical form of CJD produces the classic histologic triad of neuronal loss, astrocytic proliferation, and cytoplasmic vacuoles in neurons and astrocytes (**status spongiosus**), all in the absence of an inflammatory response. There is a predilection for cerebral cortex and basal ganglia, but all parts of the CNS may be involved. In 5-10% of cases, these changes are accompanied by the deposition of amyloid plaques. Immunostaining for PrP^{res} is definitive.

Table 16-12 Operating room sterilization procedures for CJD[85]

• Fully effective (recommended) procedures A. steam autoclaving for 1 hr at 132°C, or B. immersion in 1N sodium hydroxide (NaOH) for 1 hr at room temperature
• Partially effective procedures A. steam autoclaving at either 121° C or 132° C for 15-30 mins, or B. immersion in 1N NaOH for 15 mins, or lower concentrations (< 0.5N) for 1 hr at room temp, or C. immersion in sodium hypochlorite (household bleach) undiluted or up to 1:10 dilution (0.5%) for 1 hr[86]
• ✖ Ineffective procedures: boiling, UV or ionizing radiation, ethylene oxide, ethanol, formalin, beta-propiolactone, detergents, quaternary ammonium compounds, Lysol®, alcoholic iodine, acetone, potassium permanganate, routine autoclaving

Presentation

One third initially express vague feelings of fatigue, sleep disorders, or reduced appetite. Another third have neurologic symptoms including memory loss, confusion, or uncharacteristic behavior. The last third have focal signs including cerebellar ataxia, aphasia, visual deficits (including cortical blindness), or hemiparesis.

The typical course is inexorable, progression of dementia, often noticeably worse week by week, with subsequent rapid development of pyramidal tract findings (limb weakness and stiffness, pathologic reflexes), and late

extrapyramidal findings (tremor, rigidity, dysarthria, bradykinesia) and myoclonus (often stimulus triggered). Clinical signs of sporadic CJD are shown in *Table 16-13*.

Supranuclear gaze palsy is an occasional finding, also usually late[83]. In early stages, CJD may resemble Alzheimer's disease **(SDAT)**. 10% of cases present as ataxia without dementia or myoclonus. Cases with pre-dominant spinal cord findings may be initially mistaken for ALS.

Myoclonus subsides in the terminal phases, and akinetic mutism ensues.

Table 16-13 Major clinical signs in sporadic CJD[78]

Sign	Freq (%)
cognitive deficits*	100
myoclonus	> 80
pyramidal tract signs	> 50
cerebellar signs	> 50
extrapyramidal signs	> 50
cortical visual deficits	> 20
abnormal extraocular movements	> 20
lower motor-neuron signs	< 20
vestibular dysfunction	< 20
seizures	< 20
sensory deficits	< 20
autonomic abnormalities	< 20

* dementia, psychiatric and behavioral abnormalities

Diagnosis

The complete "diagnostic triad" (dementia, myoclonus and periodic EEG activity) may be absent in up to 25% of cases. Diagnostic criteria have been published[90] as shown in *Table 16-14*. No patients in their series with a diagnosis other than CJD fulfilled the criteria for clinically definite CJD. The most common condition other than CJD fulfilling the criteria for clinically probable CJD was SDAT (especially difficult to distinguish in the early stages). There is a *CSF* immunoassay for the 14-3-3 brain protein (*see below*).

Differential diagnosis

CSF examination to exclude infections such as tertiary syphilis or SSPE is recommended. Toxicity from bismuth, bromides and lithium must be ruledout. Myoclonus is usually more prominent early in toxic/metabolic disorders than in CJD, and seizures in CJD are usually late[78].

Table 16-14 Diagnostic criteria* of CJD[90]

• **Pathologically confirmed** (with unequivocal spongiform changes) A. clinically: requires brain biopsy (*see text*) B. found at autopsy					
Clinical criteria	Mental deterio-ration	Myo-clo-nus	1-2 Hz pe-riodic EEG complexes	Any move-ment disorder or periodic EEG activity	Duration of illness (months)
clinically definite	+	+	+		< 12
clinically probable	+	+ OR	+		< 18
clinically possible	+			+	< 24

* in patients with normal metabolic status and spinal fluid. If there are early cerebellar or visual symptoms and then muscular rigidity, or if another family member has died of pathologically verified CJD, then upgrade the degree of certainty to the next higher category

Diagnostic tests

- **imaging**: no characteristic CT or MR finding. These studies are frequently normal, but are essential to rule-out other conditions (e.g. herpes-simplex encephalitis, recent stroke…). Diffuse atrophy may be present, especially late. MRI may show increased intensity on T2WI in areas typically involved (basal ganglion, striatum) in up to 79% of cases (retrospectively)[91]. This is nonspecific but may help differentiate CJD from SDAT[92]
- **blood tests**: serum assays for S-100 protein are so insensitive and nonspecific[93] that it can only be used as an diagnostic adjunct
- **CSF**:
    - A. routine labs: usually normal, although protein may occasionally be elevated
    - B. abnormal proteins:
        1. abnormal proteins (130 & 131) have been identified in the CSF of patients with CJD[94], but the assay is technically difficult
        2. proteins 130/131 were identified as the <u>normal</u> neuronal protein 14-3-3, and a relatively simple immunoassay for this was developed for use on as little as 50 µl of CSF[95]. Detection of the 14-3-3 protein in the CSF has 96% sensitivity and specificity for

CJD among patients with dementia. False positives may occur in other conditions involving extensive neuronal destruction including: acute CVA, herpes encephalitis, multi-infarct dementia, primary CNS lymphoma and rarely SDAT (most cases of SDAT test negative). Requires CSF (cannot be done on blood)

- **EEG**: characteristic finding of bilateral, symmetrical, periodic bi- or triphasic synchronous sharp-wave complexes, AKA **periodic spikes**, AKA pseudoperiodic sharp-wave complexes (0.5-2 per second) have ≈ 70% sensitivity and 86% specificity[96]. They resemble PLEDs (*see page 266*), but are responsive to noxious stimulus (may be absent in familial CJD[83] and in the recent UK variant (*see above*))
- **SPECT scan**: may be abnormal in vCJD even when EEG is normal[97], however the findings are not specific for vCJD
- **brain biopsy**: *see below*
- **tonsillar biopsy**: patients with variant CJD (vCJD) may have detectable levels of variant type 4 of the abnormal prion protein (PrPSc) in their lymphoreticular system, which may be accessed by a 1 cm wedge-biopsy of one palatine tonsil (using careful aseptic precautions)[98]

Brain biopsy

Due to lack of an effective treatment and the potential for iatrogenic infection in surgery, biopsy is reserved for cases where establishing the diagnosis is deemed important, or as part of a research study[74], or when diagnostic tests are equivocal and other potentially treatable etiologies are suspected.

Technique: to prevent aerosolization of the infectious agent, a manual saw is recommended over a power craniotome, and every effort should be made to avoid cutting the dura with the saw. Recommended decontamination procedures should be followed (*see Table 16-12 and references*). Specimens should be clearly labeled as being from suspected CJD patients to alert laboratory personnel to the hazard. Tissue should be fixed in a saturated 15% phenolized formalin (15 g of phenol per dl of 10% neutral buffered formalin with the undissolved phenol layering at the bottom of the solution)[99].

Treatment and prognosis

Given the lack of demonstrated infectivity (with tissues other than brain or CSF), isolation precautions such as gowns or masks are felt to be unnecessary[78].

There is no known treatment. The disease is rapidly progressive. Median survival is 5 months, and 80% of patients with sporadic CJD die within 1 year of diagnosis[78].

16.10. Neurologic manifestations of AIDS

TYPES OF NEUROLOGIC INVOLVEMENT

40-60% of all patients with acquired immunodeficiency syndrome **(AIDS)** will develop neurologic symptoms, with one third of these presenting initially with their neurologic complaint[100, 101]. Only ≈ 5% of patients that die with AIDS have a normal brain on autopsy. One study found the CNS complications of AIDS shown in *Table 16-15*.

The most common conditions producing focal CNS lesions in AIDS[103]:

1. toxoplasmosis
2. primary CNS lymphoma
3. progressive multifocal leukoencephalopathy **(PML)**
4. cryptococcal abscess

Manifestations of CNS toxoplasmosis

1. mass lesion (toxoplasmosis abscess): the most common lesion causing mass effect in AIDS patients (70-80% of cerebral mass lesions in AIDS[104]) (*see below* for CT/MRI findings)
2. meningoencephalitis
3. encephalopathy

CNS toxoplasmosis occurs late in the course of HIV infection, usually when CD4 counts are < 200 cells/mm^3.

Primary CNS lymphoma (PCNSL)

Occurs in ≈ 10% of patients with AIDS[105]. PCNSL is associated with the Epstein-Barr virus (*see page 673*).

Table 16-15 CNS complications of AIDS (320 patients[100])

Complication	%
viral syndromes	
subacute encephalitis*	17
atypical aseptic meningitis	6.5
herpes simplex encephalitis	2.8
★ progressive multifocal leukoencephalopathy **(PML)**	1.9†
viral myelitis	0.93
varicella zoster encephalitis	0.31
non-viral infections	
★ *Toxoplasma gondii*	> 32
Cryptococcus neoformans	13
Candida albicans	1.9
coccidiomycosis	0.31
Treponema pallidum	0.62
atypical *Mycobacteria*	1.9
Mycobacterium tuberculosis	0.31
Aspergillus fumigatus	0.31
bacteria (*E. coli*)	0.31
neoplasms	
★ primary CNS lymphoma	4.7
systemic lymphoma with CNS involvement	3.8
Kaposi's sarcoma (including brain mets)	0.93
CVA (stroke)	
infarct	1.6
intracerebral hemorrhage	1.2
miscellaneous/unknown	7.8

* CMV encephalitis occasionally occurs

† more recent estimate[102] of the incidence of PML in AIDS: 4%

Features of PML

1. caused by a ubiquitous polyomavirus (a subgroup of papova virus, small nonenveloped viruses with a closed circular double DNA-stranded

genome) called “JC virus[A]” **(JCV)**. 60-80% of adults have antibodies to JCV[106]

2. frequently manifests in patients with suppressed immune systems, including
   A. AIDS: currently the most common underlying disease associated with PML
   B. prior to AIDS, the most common associated diseases were chronic lymphocytic leukemia & lymphoma
   C. allograft recipients: due to immunosuppression[107]
   D. chronic steroid therapy
   E. PML also occurs with other malignancies, and with autoimmune disorders (e.g. SLE)
3. pathologic findings: focal myelin loss (demyelination, ∴ affects white matter) with sparing of axon cylinders, surrounded by enlarged astrocytes and bizarre oligodendroglial cells with eosinophilic intranuclear inclusion bodies. EM can detect the virus. Sometimes occurs in brainstem and cerebellum
4. clinical findings: mental status changes, blindness, aphasia, progressive cranial nerve, motor, or sensory deficits and ultimately coma. Seizures are rare
5. imaging findings: *see below*
6. clinical course: usually rapidly progressive to death within a few months, occasionally longer survival occurs inexplicably[108]. There is no effective treatment. Some promise initially with anti-retroviral therapy[109]
7. definitive diagnosis requires brain biopsy (sensitivity: 40-96%) although it is infrequently employed. JCV has been isolated from brain and urine. Polymerase chain reaction (PCR) of JCV DNA from CSF has been reported, and is specific but not sensitive for PML

A. named after the initials of the patient in whom it was first discovered, not to be confused with Jakob-Creutzfeldt (a prion disease) nor with Jamestown Canyon virus (also confusingly called JC virus, (a single-stranded RNA virus that occasionally causes *encephalitis* in humans)

Primary effects of AIDS infection

Neurologic involvement with infection with the Human Immunodeficiency Virus **(HIV)** (aside from opportunistic infection and tumors caused by the

immunodeficient state) includes:

1. **AIDS encephalopathy**: the most common neurologic involvement, occurs in ≈ 66% of patients with AIDS involving the CNS
2. AIDS dementia AKA HIV dementia complex
3. aseptic meningitis
4. cranial neuropathies: including "Bell's palsy" (occasionally bilateral)
5. AIDS related myelopathy: vacuolization of spinal cord (see *Myelopathy*, page 1185)
6. peripheral neuropathies

Neurosyphilis

1. AIDS patients can develop neurosyphilis as little as 4 mos from infection[110] (unlike the 15-20 yrs usually required in non-immunocompromised patients)
2. neurosyphilis can develop in spite of what would otherwise be adequate treatment for early syphilis with benzathine PCN[110, 111]
3. the CDC recommends treating patients having symptomatic or asymptomatic neurosyphilis for at least 10 days with probenecid 500 mg PO QID plus either aqueous crystalline PCN-G, 2-4-million units IV q 4 hrs (total of 12-24-million units/d), or aqueous procaine PCN-G 2.4-million units IM q d. This 10 day regimen should be followed by benzathine PCN 2.4-million units IM q week **x** 3 weeks. Benzathine PCN is NOT recommended initially[112]

Neuroradiologic findings in AIDS

A series of 200 consecutive AIDS patients[113] with neurologic symptoms followed to biopsy, autopsy, or for 2 yrs showed the following on initial CT:

- 81 patients (40%) had initially normal CT, only 5% of which went on to develop progression of neurologic abnormalities or developed CT abnormalities
- 75 patients (38%) showed only diffuse cerebral atrophy; 5 of these subsequently developed focal CT findings shown to be *Toxoplasma gondii* infection
- 44 patients (22%) had ≥ 1 focal lesion

See *Table 16-16* for a comparison of neuroradiologic findings in

toxoplasmosis, PCNSL and PML.

CT/MRI findings in toxoplasma abscess

1. most common findings: large area (low density on CT) with mild to moderate edema, ring enhancement with IV contrast in 68% compatible with abscess (of those that did not ring enhance, many showed hypodense areas with less mass effect with slight enhancement adjacent to lesion), well circumscribed margins[114]
2. most commonly located in basal ganglia, are also often subcortical
3. often multiple (typically > 5 lesions[115]) and bilateral
4. usually with little to moderate mass effect[103] (in BG, may compress third ventricle and sylvian aqueduct causing obstructive hydrocephalus)
5. most patients with toxoplasmosis had evidence of cerebral atrophy

Table 16-16 Comparison of neuroradiologic lesions in AIDS*

Feature	Toxo	PCNSL	PML
Multiplicity	usually > 5	multiple but < 5	may be multiple
Enhancement	ring	homogeneous	none
Location	basal ganglia and grey-white junction	subependymal	usually limited to white matter
Mass effect	mild-moderate	mild	none-minimal
Miscellaneous	lesions surrounded by edema	may extend across corpus callosum	high signal on T2WI, low on T1WI

* abbreviations: Toxo = toxoplasmosis, PCNSL = primary CNS lymphoma, PML = progressive multifocal leukoencephalopathy

CT/MRI findings in PML (*see Table 16-16*)

Note: the appearance of PML may differ in AIDS patients from non-AIDS patients.

1. CT: diffuse areas of low density. MRI: high intensity on T2WI
2. normally involves only white matter (spares cortex), however in AIDS patients gray matter involvement has been reported
3. no enhancement (on either CT or MRI), unlike most toxoplasmosis lesions
4. no mass effect
5. no edema
6. lesions may be solitary on 36% of CTs and on 13% of MRIs

7. borders are usually more ill-defined than in toxoplasmosis[114]

CT/MRI findings in primary CNS lymphoma (PCNSL) (*see Table 16-16*)

NB: the appearance of PCNSL may differ in AIDS patients from non-AIDS patients.

1. multiple lesions with mild mass effect and edema that tend to ring-enhance on CT, or appear as areas of hypointensity surrounding central area of high intensity (target lesion) targets onT2WI MRI (unlike non-AIDS cases which tend to enhance homogeneously[116])
2. there is a greater tendency to multicentricity in AIDS patients than in the nonimmunosuppressed population[117]

Imaging recommendations

MR with gadolinium is recommended as the initial screening procedure of choice for AIDS patients with CNS symptoms (lower false negative rate than CT[103]).

MANAGEMENT OF INTRACEREBRAL LESIONS

Neurosurgical consultation is often requested for biopsy in an AIDS patient with questionable lesion(s). The diagnostic dilemma is usually for low density lesions on CT, and in the United States is primarily between the following:

- toxoplasmosis: treated with pyrimethamine and sulfadiazine (*see below*)
- PML: no proven effective treatment (antiretroviral therapy may help[109])
- CNS lymphoma: usually treated with RTX (see *CNS lymphoma*, page 672)
- TB: tends to be unlikely except in Haitian population
- note: cryptococcus is more common than PML or lymphoma, but usually manifests as cryptococcal meningitis (and not as a ring enhancing lesion) (*see page 374*)

RECOMMENDATIONS

PML can usually be identified radiographically. However, radiographic imaging alone cannot reliably differentiate toxoplasmosis from lymphoma or from some other concurrent conditions (patients with toxoplasmosis may have other simultaneous diseases). Therefore, the following recommendations are

made:

1. obtain baseline toxoplasmosis titer on all known AIDS patients (NB: 50% of the general population have been infected by toxo and have positive titer by age 6 years, 80-90% will be positive by middle adulthood). The chances of toxo are higher with serum antibodies > 1:16115 (most are > 1:256)
2. multiple enhancing lesions with basal ganglion involvement in a patient whose toxo titer changes from negative to positive have a high probability of being toxo
3. primary CNS lymphoma **(PCNSL)**
   A. with <u>single</u> lesions, lymphoma is more likely than toxo
   B. if possibility of PCNSL is strong
      1. consider LP (contraindicated in presence of mass effect)
         a. high volume LP for cytology: PCNSL can be diagnosed in ≈ 10-25% of cases using ≈ 10 ml of CSF (*see page 674* for more details)
         b. or send CSF for polymerase chain reaction **(PCR)** amplification of viral DNA of Epstein-Barr virus or JC-virus[118] (the agents responsible for AIDS-related PCNSL and PML, respectively)
      2. some recommend early biopsy[A] to identify PCNSL cases to avoid delaying RTX for 3 weeks while assessing response to antibiotics[103]
4. in patient with possible toxoplasmosis (i.e. positive toxo titer and CT findings not atypical for toxo) even if other conditions have not been excluded:
   A. empirically start: pyrimethamine (Daraprim®) (200 mg loading dose, then 75-100 mg/d), sulfadiazine (75 mg/kg PO loading dose, then 25 mg/kg q 6 hrs), folic acid (5-40 mg/d, usually 10 mg with each dose of pyrimethamine)
   B. if sulfa allergy develops (which commonly occurs), change sulfadiazine to clindamicin 400-600 mg PO or 600 mg IV q 6 hrs
   C. alternatives for complete intolerance:
      1. spiramycin (Rovamycine®) 3-4 gms/d (peds: 50-100 mg/kg/d **x** 3-4 wks)
      2. atovaquone
   D. there should be a clinical and radiographic response within 2-3 weeks[119]

E. if response is good, reduce dosage after 6-12 weeks to 50% of the above doses and maintain for life

F. if these drugs are continued, it should be possible to maintain control for remainder of patient's life (cure is not generally possible)

G. if no response to therapy after 3 weeks (some recommend 7-10 days[120]), then consider biopsy[A]

5. perform biopsy in the following settings:

A. in patient with a negative toxo titer (note: patients occasionally have negative titer because of anergy)

B. accessible lesion(s) atypical for toxo (i.e. non-enhancing, sparing basal ganglia, periventricular location)

C. in the presence of extraneural infections or malignancies that may involve the CNS

D. lesion that could be either lymphoma or toxo (e.g. single lesion, *see 3. A.*)

E. in patients who have lesions not inconsistent with toxo but fail to respond to appropriate anti-toxo medications in the recommended time (*see above*)

F. the role of biopsy for <u>non-enhancing</u> lesions is less well defined as the diagnosis does not influence therapy (most are PML or biopsies are non-diagnostic), it may be useful only for prognostic purposes[120]

G. note: the risk of open biopsy in AIDS patients may be higher than nonimmunocompromised patients. Stereotactic biopsy may be especially well suited, with up to 96% efficacy, fairly low morbidity (major risk: significant hemorrhage, ≈ 8% incidence) and low mortality[121, 122]

6. stereotactic biopsy guidelines:

A. if multiple lesions are present, choose the most accessible lesion in the least eloquent brain area, or the lesion not responding to treatment

B. biopsy the center of non-enhancing lesions, or the enhancing portion of ring-enhancing lesions

C. recommended studies on biopsy: histology; immunoperoxidase stain for *Toxoplasma gondii*; stains for TB and fungus; culture for TB, fungi, pyogens

A. instead of biopsy, a few centers advocate empiric radiation treatment (for possible lymphoma)

PROGNOSIS

Patients with CNS toxo have a median survival of 446 days, which is similar to that with PML but longer than AIDS-related PCNSL[115]. Patients with CNS lymphoma in AIDS survive on average a shorter time than similarly treated CNS lymphoma in nonimmunosuppressed patients (3 months vs. 13.5 mos). Median survival is < 1 month with no treatment. CNS lymphoma in AIDS tends to occur late in the disease, and patients often die of unrelated causes (e.g. *Pneumocystis carinii* pneumonia)[120].

16.11. Lyme disease - neurologic manifestations

Lyme disease **(LD)** is a complex multisystem disease caused by various species of Borrelia spirochetes (in North America: *Borrelia burgdorferi*) transmitted to humans by the *Ixodes scapularis* or *pacificus* ticks (the American dog tick is not involved). It was first recognized in Lyme, Connecticut in 1975, and is now the most common arthropod-borne infection in the U.S.[123].

CLINICAL FINDINGS

There are 3 clinical stages which can overlap or occur separately.

Stage 1 (early localized disease, erythema migrans and flu-like illness)

Systemic signs of infection usually begin with a flu-like illness within days to weeks of infection, symptoms include: fever, chills, malaise, fatigue or lethargy, backache, headache, arthralgia, and myalgia. Regional or generalized lymphadenopathy may occur.

The hallmark of LD is **erythema chronicum migrans (ECM)** (classically a “bullseye rash”) which begins 3-30 days after the tick bite, and occurs in 60-75% of patients. ECM usually begins in the thigh, inguinal region, or axilla, and consists of an expanding macular rash with bright red borders and central clearing and induration that usually fades without scarring in 3-4 weeks. Within 30 days of the tick bite, spirochetes may be demonstrated in acellular spinal fluid.

Stage 2 (early disseminated disease)

Several weeks to months after infection, untreated patients develop more serious organ involvement. Cardiac and neurologic involvement may occur. Manifestations include:

1. cardiac: occurs in 8%. Conduction defects (usually A-V block, generally brief and mild) and myopericarditis
2. ocular: panophthalmitis, ischemic optic atrophy, and interstitial keratitis occur rarely
3. neurologic: occurs in 10-15% of patients with stage 2 disease
   A. the clinical triad of neurologic manifestations of Lyme disease is[124]:
      - cranial neuritis (especially that mimicking Bell's palsy: Lyme disease is the most common cause of bilateral "Bell's palsy" (facial diplegia) in endemic areas)
      - meningitis
      - radiculopathy

   B. other possible neurologic involvement includes: encephalitis, myelitis, peripheral neuritis

Neurologic findings are frequently migratory, and ≈ 60% of patients have multiple neurologic findings simultaneously. In Europe, **Bannwarth's syndrome** (chronic lymphocytic meningitis, peripheral neuropathy, and radiculopathy) is the most common manifestation, and primarily affects the peripheral nervous system[125]. Neurologic symptoms usually resolve gradually.

Stage 3 (late disease)

Arthritis and chronic neurologic syndromes may occur in this stage. Arthralgias are common in stage 1, but true *arthritis* usually does not begin for months to years after infection, and is seen in ≈ 60% of cases[126]. When arthritis occurs, it may affect the knee (89%), hip (9%), shoulder (9%), ankle (7%) and/or elbow (2%)[127]. Neurologic involvement includes[128]:

1. encephalopathy[A]
2. encephalomyelitis[A]
3. peripheral neuropathy[A]
4. ataxia
5. dementia
6. sleep disorder

7. neuropsychiatric disease and fatigue syndromes

A. these conditions are chronic, and their manifestation may be subtle

DIAGNOSIS

There is no test indicative of active infection. The spirochete is difficult to culture from infected humans. Diagnosis is easy if a history of travel to endemic areas, tick bite, and ECM are identified. *Table 16-17* shows the CDC criteria for diagnosis.

Serology

It takes 7-10 days from initial infection to develop antibodies to *B. burgdorferi*, but it takes ≈ 2-3 wks before antibodies can reliably be detected in un-treated patients (antibiotics can reduce the immune response)[130]. If the first serum test is negative, it should be repeated in 4-6 weeks if the clinical suspicion of LD is strong (seroconversion from negative to positive is supportive of *B. burgdorferi* infection). False positives can occur with other borrelial and treponemal infections (e.g. syphilis, however, VDRL test will differentiate the two).

Enzyme-linked immunosorbent assay **(ELISA)** detects IgM or IgG. Antibodies to *B. burgdorferi* is the usual test method. IgM is elevated acutely, and IgG gradually rises and is elevated in almost all patients at 4-6 weeks and is usually highest in patients with arthritis[123]. Western blot may help identify false-positive ELISA results (more sensitive and specific than ELISA, however, results may vary between labs). Amplification of *B. burgdorferi* DNA by polymerase chain reaction **(PCR)** yields a more very sensitive test that may have significant false positives, and can be positive even if the DNA is from dead organisms.

Table 16-17 CDC criteria for diagnosis of Lyme disease[129]

In endemic area: • erythema chronicum migrans **(ECM)** • antibody titer ≥ 1:256 by IFA* and involvement of ≥ 1 organ system†
In non-endemic area: • ECM with antibody titer ≥ 1:256 • ECM with involvement of ≥ 2 organ systems†

• antibody titer ≥ 1:256 by IFA* and involvement of ≥ 1 organ system

* IFA = immunofluorescence antibody

† either musculoskeletal, neurologic or cardiac

CSF

Elevated CSF IgG antibody titer to *B. burgdorferi* may occur with neurologic involvement[131]. CSF findings in late disease are usually compatible with aseptic meningitis. Oligoclonal bands and increased ratio of IgG to albumin may occur[132].

Treatment[128, 133, 134]

Antibiotic therapy is more effective early in the illness.

16.12. Parasitic infections of the CNS

Many parasitic infections may involve the central nervous system. Immunosuppression (including HIV) increases the susceptibility[135]. CNS parasitic infections include (those that potentially involve neurosurgical intervention have a dagger (†):

1. cysticercosis†: see *Neurocysticercosis* below
2. toxoplasmosis†: may occur as a congenital TORCH infection, or in the adult usually with AIDS (see *Neurologic manifestations of AIDS*, page 364). *Toxoplasma gondii* is an obligate intracellular protozoan that is ubiquitous but does not cause clinical infection except in immunocompromised hosts. Histologic features: necrosis containing 2-3 nm tachyzoites (cysts)
3. echinococcus†: *see page 373*
4. amebiasis†: ≈ exclusively *Naegleria fowleri* (*see page 375*)
5. schistosomiasis
6. malaria
7. African trypanosomiasis

† parasitic infections with a dagger are those that are more likely to come to neurosurgical attention

16.12.1. Neurocysticercosis

Key concepts:

- intracranial encystment of larva of *Taenia solium* (pork tapeworm)
- the most common parasitic infection of the CNS
- neurological symptoms: seizures or progressive intracranial hypertension
- occurs from ingesting the parasite's *eggs*, not from eating infested meat
- characteristic imaging finding: low density cysts with eccentric punctate high density (the scolex = tapeworm head). Hydrocephalus is common
- medical treatment: all patients get steroids. Start antihelmintic drugs (praziquantel or albendazole) when no signs of intracranial hypertension
- biopsy sometimes needed for diagnosis. Surgery: may be required for spinal, intraventricular or subarachnoid cysts (more refractory to medical therapy) or for giant cysts (> 50 mm) when intracranial hypertension persists despite steroids

Cysticercosis is the most common parasitic infection involving the CNS[136] and is the most common cause of acquired epilepsy in low-income countries[137]. It is caused by *Cysticercus cellulosae*, the larval stage of the pork tapeworm *Taenia solium*, which has a marked predilection for neural tissue. Cysticercosis is endemic in areas of Mexico, Eastern Europe, Asia, Central and South America, and Africa. The incidence of neurocysticercosis (encystment of larva in the brain) may reach 4% in some areas[138]. The incubation period varies from months to decades, but 83% of cases show symptoms within 7 years of exposure.

Life cycle of T. solium

There are 3 stages to the life cycle: larva, embryo (or oncosphere) and adult. *T. solium* can infect man in two different ways: as the adult worm or as the larva.

Infection with the adult worm (taeniasis - a parasitic infection)

Human intestinal tapeworm infection (taeniasis) results from eating undercooked infested (measly) pork. The encysted larvae are released in the small bowel and can then mature within the intestine into an adult over about 2 months. The scolex (head) of the segmented adult worm attaches by means of

four suckers and two rows of hooklets to the wall of the small intestine where the worm absorbs food directly through its cuticle. Man is the only known definitive host for the adult tapeworm, for which the GI tract is the sole habitat. Proglottids (mature segments, each containing reproductive organs) produce eggs which are liberally excreted along with gravid proglottid segments in the feces.

Infection with the larva

The disease cysticercosis occurs when animals or humans become an intermediate host for the *larval* stage by ingesting viable eggs produced by the proglottid. The most common routes of ingestion of viable eggs are:

1. food (usually vegetables) or water contaminated with human feces containing eggs or gravid proglottids (this is the means whereby pigs acquire the disease)
2. fecal-oral autoinoculation in an individual harboring the adult form of the tape-worm due to lack of good sanitary habits or facilities
3. autoinfection by reverse peristalsis of gravid proglottids from the intestine into the stomach (unproven theoretical possibility)

In the duodenum of man and pig, the shell of the ova dissolves and the thusly hatched embryos (oncospheres) burrow through the small bowel wall to enter the lymphatics or systemic circulation and gain access to:

- brain: involved in 60-92% of cases of cysticercosis. Latency from ingestion of eggs to *symptomatic* neurocysticercosis: 2-5 years[139]
- skeletal muscle
- eye: immunologically privileged, like brain
- subcutaneous tissue
- heart

Once in the tissue of the intermediary host, embryos develop a cyst wall in ≈ 2 months (immature cyst) which matures in ≈ 4 months to a larva. Larval cysts are usually rapidly eliminated by the immune system. Many larvae die naturally within 5-7 yrs or with cysticidal therapy producing an inflammatory reaction with collapse of the cyst (**granular nodular stage**), these sometimes calcify (nodular calcified stage). In pigs, the larva lie dormant in the muscle, “waiting” to be eaten after which the cycle repeats.

Types of neurologic involvement

Spinal cord and peripheral nerves involvement is rare.

Giant cysts: definition: cyst with diameter > 50 mm[140].

Two types of cysts tend to develop in the brain[141]:

1. **cysticercus cellulosae**: regular, round or oval thin-walled cyst, ranging in size from ≈ 3 to 20 mm tending to form in the parenchyma or narrow subarachnoid spaces. This cyst contains a scolex (head), is usually static, and produces only mild inflammation during the active phase
2. **cysticercus racemosus**: larger (4-12 cm), grows actively producing grape-like clusters in the basal subarachnoid spaces and produces intense inflammation. There are no larvae in these cysts. These cysts usually degenerate in 2-5 years, in which the capsule thickens and the clear cyst contents are replace by a whitish gel which undergoes calcium deposition with concomitant shrinkage of the cyst

Location of the cysts tends to fall into 1 of 4 groups:

1. meningeal: found in 27-56% of cases with neural involvement. Cysts are adherent or free-floating and are located either in:
   - dorsolateral subarachnoid space: usually C. cellulosae type, causing minimal symptoms
   - basal subarachnoid space: usually the expanding C. racemosus form producing arachnoiditis and fibrosis comprising a chronic meningitis with hypoglycorrhachia. Can obstruct foramina of Luschka and Magendie producing hydrocephalus, or can cause entrapment of basal cisterns → cranial neuropathies (including visual disturbance). Extremely high mortality with this form
2. parenchymal: found in 30-63%; focal or generalized seizures occurs in ≈ 50% of cases (up to 92% in some series)
3. ventricular: found in 12-18%, possibly gaining access via the choroid plexus. Pedunculated or free floating cysts occur, can block CSF flow and cause hydrocephalus with intermittent intracranial hypertension (Brun syndrome). There may be adjacent ependymal enhancement (ependymitis)
4. mixed lesions: found in ≈ 23%

Clinical

Presentation: seizures, signs of elevated ICP, focal deficits related to the location of the cyst, and altered mental status are the most common findings. Increased ICP may be due to hydrocephalus or to giant cysts. Symptoms may also be produced by the immunologic reaction to the infestation (cysticercotic

encephalitis). Cranial nerve palsies can occur with basal arachnoiditis. Subcutaneous nodules may sometimes be felt.

DIAGNOSIS

Diagnosis is usually made by imaging studies and confirmatory serologic tests.

LABORATORY EVALUATION

Mild peripheral eosinophilia can occur, but is inconsistent and thus unreliable.

CSF may be normal. Eosinophils are seen in 12-60% of cases and suggests parasitic infection. Protein may be elevated.

Stool: less than 33% of cases have *T. solium* ova in the stool.

Serology

Most centers use enzyme-linked immunoelectrotransfer blot **(EIBT)** against glycoprotein *antigens* (western blot) which is ≈ 100% specific and 98% sensitive[142], although sensitivity is less (70%) in cases with a solitary cyst[143]. May be used on serum or CSF. EIBT has effectively superseded ELISA where titer is considered significant at 1:64 in serum, and 1:8 in the CSF; checking for titer exceeding these thresholds in the serum produces a test that is more sensitive and in the CSF is more specific for cysticercosis. False negative rates are higher in cases without meningitis.

RADIOGRAPHIC EVALUATION

Soft-tissue x-rays may show calcifications in subcutaneous nodules, and in thigh and shoulder muscles.

Skull x-rays show calcifications in 13-15% of cases with neurocysticercosis. May be single or multiple. Usually circular or oval in shape.

CT

The following findings on brain CT have been described (modified[141, 144]):

1. ring enhancing cysts of various sizes representing living cysticerci. Little inflammatory response (edema) occurs as long as larva is alive. Characteristic finding: small (< 2.5 cm) low density cysts with eccentric punctate high density that may represent the scolex

2. low density with ring enhancement seen as an intermediate stage between living cyst and calcified remnant representing intermediate stage in granuloma formation. Resultant inflammatory reaction can cause edema, and basal arachnoiditis in cysts located in basal subarachnoid space. Often ring enhancing
3. intraparenchymal punctate calcifications (granuloma) sometimes with, but usually without surrounding enhancement, seen with dead parasites
4. hydrocephalus. Sometimes with intraventricular cysts which may be isointense with CSF on plain CT[145] and may require contrast CT ventriculography[146] or MRI to be demonstrated

MRI

Early findings: nonenhancing cystic structure(s) with eccentric T1WI hyperintensity (scolex) with no inflammatory response. Lesions may be seen in parenchyma, ventricle, and subarachnoid space. The cyst collapses in later stages of parasitic evolution, with initial edema that gradually resolves with time.

TREATMENT

Combination of:

1. antihelmintic medication: antiparasitic and/or cysticidal regimens
2. antiepileptics: to treat seizures, which may sometimes be medically refractory
3. steroids (*see below*)
4. surgery:
   A. surgical resection of lesions when appropriate
   B. ventricular CSF diversionary procedures

Steroids

Corticosteroids should be used in all patients. May temporarily relieve symptoms, and may help decrease edema that tends to occur initially during treatment with anti-helmintic drugs. If possible, start 2-3 d before antihelmintics (e.g. dexamethasone 8 mg q 8 hours[140]), on day 3 decrease to 4 mg q 8 hours, on day 6 change to prednisone 0.4 mg/kg per day divided TID. Taper steroids after antihelmintics are discontinued. In patients with symptoms of intracranial hypertension: antihelmintic treatment is started after symptoms subside (usually after 3 doses). ✖ Any cysticercocidal drug may cause irreversible damage when

used to treat ocular or spinal cysts, even with corticosteroid use.

Antiepileptics

Seizures usually respond to a single AED. However, the risk of seizures may be lifelong. Risk factors for recurrent seizures: calcified brain lesions, multiple seizures, multiple brain cysts[147].

Antihelmintic drugs

Praziquantel (Biltricide®) is an antihelmintic with activity against all known species of schistosomas. Several regimens have been published:

- 50 mg/kg/d divided in 3 doses (same dose for pediatrics) for 15 days (doses of 100 mg/kg/d have been recommended[140] because steroids reduce serum concentration by 50%[148]). Produces a significant reduction in symptoms and in number of cysts seen on CT[136]
- 10-100 mg/kg/d **x** 3-21 days
- high dose single day regimen: 25-30 mg/kg q 2 hrs **x** 3 doses
- for intestinal infestation: single oral dose of 5-10 mg/kg

Albendazole (Zentel®) 15 mg/kg per day divided in 2-3 doses, taken with a fatty meal to enhance absorption (same dose for pediatrics), may be given for 3 months[149, 150], can be stopped sooner if imaging shows resolution[140]. More parasiticidal than praziquantel and may have fewer side effects.

Niclosamide (Niclocide® and others) may be given orally to treat adult tapeworms in the GI tract. ***Rx*** 1 gm (2 tablets) chewed PO, repeated in 1 hour (total = 2 gm).

Intraventricular disease: There is no consensus on the efficacy of medical treatment for intraventricular cysts[140, 151, 152].

Surgery

Surgery may sometimes be necessary to establish the diagnosis. Stereotactic biopsy may be well suited for some cases, especially with deep lesions.

CSF diversion is necessary for patients with symptomatic hydrocephalus, although tubing may become obstructed by granulomatous inflammatory debris[153].

Surgery may be indicated for spinal cysts[138] and for intraventricular cysts which may be less responsive to medical therapy. The latter may sometimes be

dealt with using stereotactic techniques and/or endoscopic instrumentation[146], however, shunting and antihelmintics may suffice[152]. Surgery may also be needed for giant cysts when intracranial hypertension does not respond to steroids[140]. Antihelmintics may be required even after complete surgical removal because of possibility of relapse[140].

Follow-up

CT or MRI scan every 6 months until lesions disappear or calcify[140].

Contacts

Both patients with cysticercosis and their personal contacts should be screened for tapeworm infection since a single dose of niclosamide or praziquantel will eliminate the tapeworm[154]. Close contacts of persons with tapeworms should have screening by medical history and serologic testing for cysticercosis; if suggestive of cysticercosis a neurologic exam and CT or MRI should be done.

16.12.2. Echinococcosis

AKA **hydatid (cyst) disease**. Caused by encysted larvae of the dog tapeworm *Echinococcus granulosa* in endemic areas (Uruguay, Australia, New Zealand…). The dog is the primary definitive host of the adult worm. Intermediate hosts for the larval stage include sheep and man. Ova are excreted in dog feces and contaminate herbage eaten by sheep. After ingestion, the embryos hatch and the parasite burrows through the duodenal wall to gain hematogenous access to multiple organs (liver, lungs, heart, bone, brain). Dogs eat these infested organs and the parasite enters the intestine where it remains.

Man is infected either by eating food contaminated with ova, or by direct contact with infected dogs. CNS involvement occurs in only ≈ 3%. Produces cerebral cysts that are confined to the white matter. Primary cysts are usually solitary, secondary cysts (e.g. from embolization from cardiac cysts that rupture or from iatrogenic rupture of cerebral cysts) are usually multiple. The CT density of the cyst is similar to CSF, it does not enhance (although rim enhancement may occur if there is an inflammatory reaction), and there is little surrounding edema. It contains germinating parasitic particles called “hydatid sand” containing ≈ 400,000 scoleces/ml. The cyst enlarges slowly (rates of ≈ 1 cm per year are

quoted, but this is variable and may be higher in children), and usually does not present until quite large with findings of increased ICP, seizures, or focal deficit. Patients often have eosinophilia and may have positive serologic tests for hydatid disease.

Treatment

Treatment is surgical removal of the intact cyst. Every effort must be made to avoid rupturing these cysts during removal, or else the scoleces may contaminate the adjacent tissues with possible recurrence of multiple cysts or allergic reaction. May use adjunctive medical treatment with albendazole (Zentel®) 400 mg PO BID (pediatric dose: 15 mg/kg/d) **x** 28 days, taken with a fatty meal, repeated as necessary[150].

The Dowling technique is recommended[155]:

1. the head is positioned so that the cyst points straight up towards the ceiling when the OR table is 30° head up
2. drilling burr holes and performing craniotomy must be done very carefully to avoid rupturing the cyst or tearing the dura which is thin and under tension
3. do not coagulate with anything but low-power bipolar (to avoid cyst rupture)
4. open the dura circumferentially away from the dome of the cyst as it may be adherent to the dura
5. keep the surface of the cyst moist to prevent desiccation and rupture
6. open the thinned overlying cortex gently, separating it from the cyst with irrigation and cottonoids. The cortical opening need only be ≈ 3/4 the cyst diameter but no less
7. insert a soft rubber catheter between the cyst and the brain, and gently irrigate with saline as the head of the OR table is slowly lowered 45° while the surgeon supports the adjacent cortex with his/her fingers
8. continue irrigating more saline and float the cyst out and into a saline filled receptacle
9. if the cyst is ruptured during the procedure, immediately place a sucker in the cyst to aspirate the contents, remove the capsule, and wash the cavity with saline for 5 minutes. Change instruments and gloves. Placing 10% formalin soaked cottonoids on the cavity for a few minutes is controversial[156 (p 3750)]

16.13. Fungal infections of the CNS

Most are medically treated conditions that do not require neurosurgical intervention. They tend to present either with chronic meningitis or brain abscess. Some of the more common ones or those of particular relevance to neurosurgery include:

1. cryptococcosis: *see below*
   A. cryptococcal meningitis
   B. cryptococcoma (mucinous pseudocyst): rare
2. candidiasis: the most common fungal infection of the CNS, but rarely diagnosed before autopsy. Very rare in healthy individuals. Most are *C. albicans*
   A. candidal meningitis: the most common CNS infection (*see page 345* for Rx)
   B. parenchymal infection: candida brain abscesses are rare
   C. following ventricular shunt placement: almost all fungal VP shunt infections are due to *Candida spp.*[16] (*see page 346*)
3. aspergillosis: may be associated with cerebral abscess in organ transplant patients (*see page 351*)
4. coccidiomycosis: caused by the dimorphic fungus *Coccidioides immitis*. Endemic in southwestern U.S., Mexico, and Central America. Usually presents as meningitis, with rare reports of parenchymal lesions[157]
5. mucormycosis (phycomycosis): usually occurs in diabetics (*see page 836*)

CRYPTOCOCCAL INVOLVEMENT OF THE CNS

CNS involvement is diagnosed more frequently in living patients than any other fungal disease. Occurs in healthy or immunocompromised patients. In HIV, *Cryptococcus neoformans* is the typical agent.

1. cryptococcoma (mucinous pseudocyst): a parenchymal collection which occurs almost exclusively in AIDS patients. Much less common than cryptococcal meningitis. No enhancement of the lesion or the meninges. Usually 3-10 mm in diameter and are frequently located in the basal ganglia (due to spread by small perforating vessels)
2. cryptococcal meningitis:
   A. occurs in 4-6% of patients with AIDS[158]. Typical symptoms: fever,

malaise and H/A[159]. Meningeal signs (nuchal rigidity, photophobia…) occur in only ≈ 25%. Encephalopathic symptoms (lethargy, altered mentation…) usually from increased ICP occur in a minority

B. can also occur without AIDS: *gatti* variety can infect the brain of immuno-competent hosts[160]

C. may be associated with increased ICP (with or without hydrocephalus on CT/MRI), decreased visual acuity, and/or cranial nerve deficits. Dilation of Virchow-Robbins spaces may be seen on imaging; on MRI the signal is similar to CSF on T1WI & T2WI but will be higher signal on FLAIR

D. late deterioration in the absence of documented infection may respond to decadron 4 mg q 6 hrs transitioned to prednisone 25 mg p.o. q d[161]

Diagnosis

LP: should be done at the time of diagnosis, with OP measured in the lateral decubitus position[162]. CSF cryptococcal antigen titer is invariably high with cryptococcal meningitis or meningoencepahlitis. OP is usually elevated, and is > 20 cm H_2O in up to 75%.

Serum cryptococcal Ag: almost always elevated with CNS involvement[162].

Management

2009 CDC guidelines for CNS cryptoccal infection in HIV-infected adolescents/adults[162]:

1. antifungal agents: the recommended initial standard treatment[162] is amphotericin B deoxycholate (Amphocin®) 0.7 mg/kg IV q d, plus fluconazole (an oral triazole) 100 mg/kg po q d in 4 divided doses
2. patients with clinical signs of increased ICP (confusion, blurred vision, papilledema, LE clonus…) should have LP to measure ICP
3. management of intracranial hypertension **(ICHT)** (OP ≥ 25 cm H_2O) with or without hydrocephalus:[A]
   A. daily LPs: drain enough CSF to reduce ICP by 50% (typically 20-30 ml)[164]
   B. daily LPs may be suspended when pressures are normal for several consecutive days
   C. lumbar drain: occasionally needed for extremely high OPs (> 40 cm

H_2O) when frequent LPs are required to or fail to control symptoms[163]

D. **CSF shunt**: considered when daily LPs are no longer tolerated or when signs and symptoms of ICHT are not being relieved (neither dissemination of infection through the distal shunt nor creation of a nidus of infection refractory to medical therapy has been described[165]). Options:
   1. lumboperitoneal shunt
   2. VP or VA shunt[166, 167]

4. antifungal treatment is continued for ≥ 2 weeks if renal function is normal[B]
5. after 2 weeks of treatment, repeat the LP to look for clearance of the organism from the CSF. Positive CSF cultures after 2 weeks of treatment are predictive of future relapse and are associated with worse outcome
6. treatment failures: defined as lack of clinical improvement after 2 weeks of appropriate therapy including management of ICHT, or relapse after an initial response, defined as either a positive CSF culture and/or rising CSF cryptococcal Ag titer with a compatible clinical picture. Management:
   A. optimal management has not been defined
   B. trials with alternative antifungals (e.g flucytosine) or higher doses of fluconazole
7. maintenance therapy (secondary prophylaxis): HIV patients who have completed 10 weeks of treatment should be maintained on fluconazole 200 mg q d until immune reconstitution occurs, otherwise lifetime treatment is indicated[162]
8. the risk of recurrence is low for patient who remain asymptomatic after a complete course of therapy and have sustained increase (> 6 months) of CD4+ counts to ≥ 200 cells/μL. Some experts perform an LP to document negative CSF culture and antigen before stopping maintenance therapy

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A. corticosteroids, acetazolamide and mannitol have not been shown to be effective[163]

B. most immunocompetent patients will be successfully treated with 6 weeks of therapy[163]

16.14. Amebic infections of CNS

Naegleria fowleri: the only ameba known to cause CNS infection in humans → primary amebic meningoencephalitis **(PAM)**: diffuse encephalitis with hemorrhagic necrosis and prurulent meningitis involving brain and spinal cord. Rare (only 95 cases in the U.S. as of 2002, and ≈ 200 cases worldwide as of 2004). Typically occurs ≤ 5 days of exposure, usually from diving in warm freshwater. The ameba gains entry to the CNS by invading nasal olfactory mucosa.

Associated cerebral edema may cause increased ICP and, ultimately, herniation. Fatal in ≈ 95% usually within 1 week.

CSF: cloudy and often hemorrhagic, ↑ leukocytes, ↑ protein, normal or ↓ glucose, Gram stain negative (no bacteria or fungi), wet prep → motile trophozoites (may be confused with WBCs).

Treatment

Drug of choice: amphotericin B (lipid preparations (Abelcet®) achieve higher MICs than other amphotericin preparations). Miconazole may be synergistic.

Surgical intervention: ventriculostomy with CSF drainage may be indicated when findings are suggestive of increased ICP. In one survivor, surgical drainage of a brain abscess was performed in addition to treatment with a 6-week course of amphotericin B, rifampicin, and chloramphenicol.

16.15. Spine infections

Spine infections may be divided into the following major categories:

1. vertebral osteomyelitis (spondylitis): *see page 380*
    A. pyogenic
    B. nonpyogenic, granulomatous
        1. tuberculous spondylitis
        2. brucellosis
        3. aspergillosis
        4. blastomycosis
        5. coccidiomycosis
        6. infection with *Candida tropicalis*
2. discitis: *see page 383*, usually associated with vertebral osteomyelitis (spondylodiscitis) *see page 380*

A. spontaneous
B. post-operative/post-procedure

3. spinal epidural abscess (*see below*)
4. spinal subdural empyema
5. meningitis
6. spinal cord abscess

MRI experience suggests that patients with infectious spondylitis will develop an associated epidural abscess if untreated, and that epidural empyema is unusual in the absence of vertebral osteomyelitis[168]. Thus, the discovery of one of these conditions should prompt a search for the other.

16.15.1. Spinal epidural abscess

Key concepts:

- should be considered in a patient with back pain, fever, and spine tenderness
- major risk factors: diabetes, IV drug abuse, chronic renal failure, alcoholism
- may produce progressive myelopathy, sometimes with precipitous deterioration
- fever, sweats or rigors are common, but normal WBC and temperature can occur
- classical presentation of a skin boil (furuncle) occurs in only ≈ 15%
- treatment: controversial. Many patients improve with antibiotics alone. Early surgery is advocated by some even if no neuro deficit because of risk of precipitous deterioration

Epidemiology

Incidence: 0.2-1.2 per 10,000 hospital admissions annually[169], possibly on the rise[170]. Average age: 57.5 ± 16.6 years[171].

Thoracic level is the most common site (≈ 50%), followed by lumbar (35%) then cervical (15%)[171]. 82% were posterior to the cord, and 18% anterior in one series[169]. SEA may span from 1 to 13 levels[172].

Spinal epidural abscess **(SEA)** is often associated with vertebral osteomyelitis (in one series of 40 cases, osteomyelitis occurred in all cases of anterior SEA, in 85% of circumferential SEA, and no cases of posterior SEA)

and intervertebral discitis.

CO-MORBID CONDITIONS

Chronic diseases associated with compromised immunity were identified in 65% of 40 cases[173]. Associated conditions included diabetes mellitus (32%), IV drug abuse (18%), chronic renal failure (12%), alcoholism (10%), and the following in only 1 or 2 patients: cancer, recurrent UTI, Pott's disease, and positivity for HIV. Chronic steroid use and recent spinal procedure or trauma (e.g. GSW) are also risk factors[172]. Also, skin infection.

CLINICAL FEATURES

Usually presents with excruciating pain localized over spine, tender to percussion. Radicular symptoms follow with subsequent distal cord findings, often beginning with bowel/bladder disturbance, abdominal distension, weakness progressing to para- and quadriplegia. Average time is 3 days from back pain to root symptoms; 4.5 days from root pain to weakness; 24 hrs from weakness to paraplegia.

Fever, sweats or rigors are common, but are not always present[172].

A furuncle may be identified in 15%.

Patients may be encephalopathic. This may range from mild to severe and may further delay diagnosis. Meningismus with a positive Kernig's sign may occur.

Patients with post-operative SEA may demonstrate surprisingly few signs or symptoms (including lack of leukocytosis, lack of fever) aside from local pain[174].

Pathophysiology of spinal cord dysfunction

Although some cord symptoms may be due to mechanical compression (including that due to vertebral body collapse), this is not always found[175]. A vascular mechanism has also been postulated, and various combinations of arterial and venous pathology have been described[169] (one autopsy series showed little arterial compromise, but did show venous compression and thrombosis, thrombophlebitis of epidural veins, and venous infarction and edema of the spinal cord[176]). Occasionally, there may be infection of the spinal cord itself, possibly by extension through the meninges.

Differential diagnosis

SEA should be considered in any patient with backache, fever, and spine tenderness[177]. Also see *Differential diagnosis, Myelopathy* on page 1185.

Differential diagnosis

1. meningitis
2. acute transverse myelitis (paralysis is usually more rapid, radiographic studies are normal)
3. intervertebral disc herniation
4. spinal cord tumors
5. post-op SEA may appear similar to pseudomeningocele[174]

Source site of infection

- hematogenous spread is the most common source (26-50% of cases) either to the epidural space or to the vertebra with extension to epidural space. Reported foci include:
  - A. skin infections (most common): furuncle may be found in 15% of cases
  - B. parenteral injections, especially with <u>IV drug abuse</u>[178]
  - C. bacterial endocarditis
  - D. UTI
  - E. respiratory infection (including otitis media, sinusitis, or pneumonia)
  - F. pharyngeal or dental abscess
- direct extension from:
  - A. decubitus ulcer
  - B. psoas abscess: *see below*
  - C. penetrating trauma, including: abdominal wounds, neck wounds, GSW
  - D. pharyngeal infections
  - E. mediastinitis
  - F. pyelonephritis with perinephric abscess
- following spinal procedures (3 of 8 of these patients had readily identified perioperative infections of periodonta, UTI, or AV-fistula[173])
  - A. open procedures: especially lumbar discectomy (incidence[174] ≈ 0.67%)
  - B. closed procedures: e.g. epidural catheter insertion for spinal epidural

anesthesia[179-181], lumbar puncture[182]…
- a history of recent back trauma is common (in up to 30%)
- no source can be identified in up to 50% of patients in some series[183]

Psoas abscess

1. psoas muscle:
   A. one of 2 heads of the iliopsoas muscle (the other head is iliacus)
   B. origin: inner surface of ilium, base of sacrum, and transverse processes, vertebral bodies **(VB)** and intervertebral discs of spinal column starting from the inferior margin of T12 VB, extending to the upper part of L5 VB. Insertion: lesser trochanter of the femur. Psoas is the primary hip flexor
   C. innervation: branches of L2-4 nerve roots proximal to the formation of the femoral nerve
   D. susceptibility to infection
      1. rich vascular supply makes it vulnerable to hematogenous spread
      2. proximity to structures that may be a source of infection: sigmoid colon, jejunum, vermiform appendix, ureters, aorta, renal pelvis, pancreas, iliac lymph nodes and spine
2. may be primary (no identifiable underlying disease) or secondary in which it may be associated with one of the conditions shown in *Table 16-18*
3. risk factors: IV drug abuse, HIV/AIDS, age > 65 years, DM, immunosuppression, renal failure
4. physical findings: signs of iliopsoas inflammation include:
   A. active: pain on flexing the hip against resistance
   B. passive: with the patient lying on the unaffected side, hyperextension of the affected hip stretches the psoas muscle and produces pain
5. diagnostic tests:
   A. routine infection work-up: WBC (often elevated), blood cultures, U/A + C&S (pyuria may be seen)
   B. AP abdominal x-ray: psoas shadow may be obliterated
   C. CT: sensitivity is 80-100% (MRI is not better)[185]. Enlargement of psoas muscle on affected side best seen inside iliac wing
6. treatment often includes drainage of the psoas abscess either surgically or percutaneously with CT-guidance
7. mortality rates with psoas abscess: 2.4% with primary, 19% with

secondary[186]

Table 16-18 Conditions associated with secondary psoas abscess[184]

Organ system	Condition
gastrointestinal	diverticulitis, appendicitis, Crohn's disease, colorectal cancer
genitourinary	UTI, cancer
musculoskeletal infections	vertebral osteomyelitis, infectious sacroiliitis, septic arthritis
other	endocarditis, femoral artery catheterization, infected abdominal aortic aneurysm graft, hepatocellular Ca, intrauterine contraceptive device, trauma, sepsis, dialysis (peritoneal or long-term hemodialysis)

ORGANISMS

Operative cultures are most useful in identifying the responsible organism, these cultures may be negative (possibly more common in patients previously on antibiotics) and in these cases blood cultures may be positive. No organism may be identified in 29-50% of cases.

1. *Staph. aureus*: the most common organism (cultured in > 50%) possibly due to its propensity to form abscesses, its ubiquity, and its ability to infect normal and immunocompromised hosts (these facts help explain why many SEA arise from skin foci)
2. aerobic & anaerobic streptococcus: second most common
3. *E.coli*
4. *Pseudomonas aeruginosa*
5. *Diplococcus pneumoniae*
6. *Serratia marcescens*
7. Enterobacter
8. chronic infections:
   A. TB is the most common of these, and although it has become less wide-spread in the U.S. it is still responsible for 25% of cases of SEA[187], it is usually associated with vertebral osteomyelitis (Pott's disease) (see *Tuberculous vertebral osteomyelitis*, page 381)
   B. fungal: cryptococcosis, aspergillosis, brucellosis
   C. parasitic: Echinococcus
9. multiple organisms in ≈ 10%
10. anaerobes cultured in ≈ 8%

Laboratory tests

CBC: leukocytosis common in acute group (average WBC = 16,700/mm^3), but usually normal in chronic (ave. WBC = 9,800/mm^3)[169].

ESR elevated in most[70], usually > 30[173].

LP: performed cautiously in suspected cases at a level distant to the clinically suspected site (C1-2 puncture may be needed to do myelogram) with constant aspiration while approaching thecal sac to detect pus (danger of transmitting infection to subarachnoid space); if pus is encountered, stop advancing, send the fluid for culture, and abort the procedure. CSF protein & WBC usually elevated; glucose normal (indicative of parameningeal infection). 5 of 19 cases grew organisms identical to abscess.

Blood cultures: may be helpful in identifying organism in some cases.

Anergy battery: (e.g. mumps and Candida) to assess immune system.

Radiographic studies

Plain films: Usually normal unless there is osteomyelitis of adjacent vertebral bodies (more common in infections anterior to dura). Look for lytic lesions, demineralization, and scalloping of endplates (may take 4-6 weeks after onset of infection).

MRI: Imaging study of choice. Differentiates other conditions (especially transverse myelitis or spinal cord infarction) better than myelo/CT, and doesn't require LP.

Typical findings: T1WI → hypo- or isointense epidural mass, vertebral osteomyelitis shows up as reduced signal in bone. T2WI → high intensity epidural mass that often enhances with gadolinium (3 patterns of enhancement: 1) dense homogeneous, 2) inhomogeneous with scattered areas of sparse or no uptake, and 3) thin peripheral enhancement[188]) but may show minimal enhancement in the acute stage when comprised primarily of pus with little granulation tissue. Vertebral osteomyelitis shows up as increased signal in bone, associated discitis produces increased signal in disc and loss of intranuclear cleft. Unenhanced MRI may miss some SEA[189], gadopentetate dimeglumine enhancement may slightly increase sensitivity[190].

Myelogram: Usually shows findings of extradural compression (e.g. "paintbrush appearance" when complete block is present). In the event of complete block, C1-2 puncture is needed to delineate upper extent (unless post-myelographic CT shows dye above the lesion). See cautions above regarding LP.

CT scan: Intraspinal gas has been described on plain CT[191]. Post-myelographic CT is more sensitive.

TREATMENT

Controversial. Some advocate early surgical evacuation combined with antibiotics as the treatment of choice. Argument: although there are reports of management with antibiotics alone[192-194] ± immobilization[168], rapid and irreversible deterioration has occurred even in patients treated with appropriate antibiotics who were initially neurologically intact[171, 173]. 86% of those who deteriorated were initially treated it with antibiotics alone[172]. Therefore it is recommended that nonsurgical management be reserved for the following patients (reference[192] modified[172]):

1. those with prohibitive operative risk factors
2. involvement of an extensive length of the spinal canal
3. complete paralysis for > 3 days

Surgery

Goals are establishing diagnosis and causative organism, drainage of pus and debridement of granulation tissue, and bony stabilization if necessary. Most SEA are posterior to dura and are approached with extensive laminectomy. For posteriorly located SEA and no evidence of vertebral osteomyelitis, instability will usually not follow simple laminectomy and appropriate postoperative antibiotics[183]. Closure is performed with limited wire sutures. Post-op drainage is not necessary in cases with only granulation tissue and no pus. For recurrent infections, reoperation and post-op suction-irrigation may be needed[195].

Patients with vertebral osteomyelitis may develop instability after laminectomy alone[196] especially if significant bony destruction is present. Thus for anterior SEA, usually with osteomyelitis (especially Pott's disease), a posterolateral extracavitary approach is utilized whenever possible (to avoid transabdominal or transthoracic approach in these debilitated patients) with removal of devitalized bone usually followed by posterior instrumentation and fusion. Strut grafting with autologous bone (rib or fibula) can be done acutely in Pott's disease with little risk of graft infection. With purulent osteomyelitis, metal hardware is not contraindicated but bone grafting risks continuation of infection.

Specific antibiotics

If organism and source unknown, *S. aureus* most likely. Empiric antibiotics:

1. 3rd generation cephalosporin, e.g. cefotaxime (Claforan®)

PLUS

2. vancomycin: until methicillin resistant *S. aureus* **(MRSA)** can be ruled out. Once MRSA is ruled out switch to synthetic penicillin (e.g. nafcillin or oxacillin)

PLUS

3. rifampin PO

Modify antibiotics based on culture results or knowledge of source (e.g. IV drug abusers have a higher incidence of Gram-negative organisms).

Duration of treatment

For SEA, 3-4 weeks of IV antibiotics followed by 4 weeks of oral antibiotics usually suffices. 6-8 weeks of IV antibiotics are suggested if there is documented concomitant vertebral osteomyelitis[197] (although some argue that osteomyelitis is present pathologically in most cases even if not demonstrated radiographically, and therefore there should be no treatment difference between these groups[198]). Serial ESRs may also guide duration (failure to reduce suggests residual infection[170]). Immobilization for at least 6 weeks during antibiotic therapy is recommended.

OUTCOME

Fatal in 4-31%[199] (the higher end of the range tends to be in older patients and in those paralyzed before surgery[173]). Patients with severe neurologic deficit rarely improve, even with surgical intervention within 6-12 hrs of onset of paralysis, although a few series have shown a chance for some recovery with treatment within 36 hrs of paralysis[177, 198]. Reversal of paralysis of caudal spinal cord segments if present for more than a few hours is rare (exception: Pott's disease has 50% return). Mortality is usually due to original focus of infection or as a complication of residual paraplegia (e.g. pulmonary embolism).

16.15.2. Vertebral osteomyelitis

Key concepts:

- presentation and risk factors similar to spinal epidural abscess (*see page 376*)
- percutaneous needle biopsy for C&S and to rule-out tumor. Can be done by neurosurgeon or interventional radiologist
- treatment: most cases can be managed nonsurgically with long-term antibiotics
- surgery is considered for instability, and infrequently for severe resistance to Abx

For differential diagnosis, *see Destructive lesions of the spine*, page 1232. Often associated with discitis, which may be grouped together under the term *spondylodiscitis*. VO has features similar to spinal epidural abscess **(SEA)** (*see page 376*).

Vertebral body collapse and kyphotic deformity may occur with possible retropulsion of necrotic bone and disc fragments, compressing the spinal cord or cauda equina.

Epidemiology

Vertebral osteomyelitis **(VO)** comprises 2-4% of all cases of osteomyelitis[200]. Incidence is 1:250,000 in general population. Incidence appears to be rising. Male:female ratio is 2:1. Incidence increases with age, most patients are > 50 years old. The lumbar spine is the most common site, followed by thoracic, cervical and sacrum[201]. Thoracic VO may → empyema.

Risk factors

1. IV drug abuse[202]
2. diabetes mellitus: susceptible to unusual bacterial infections and even fungal osteomyelitis
3. hemodialysis: a diagnostic challenge since radiographic changes of osteomyelitis can occur even in the absence of infection (see *Destructive lesions of the spine*, page 1232)
4. immunosuppression
   A. AIDS
   B. chronic corticosteroid use
   C. ethanol abuse
5. infectious endocarditis

6. following spinal surgery or invasive diagnostic or therapeutic procedures
7. may occur in elderly patients with no other identifiable risk factors[203]

Complications that may accrue

1. spinal epidural abscess
2. subdural abscess
3. meningitis
4. bony instability
5. progressive neurologic impairment
6. unique to cervical spine involvement: pharyngeal abscess
7. unique to thoracic spine involvement: mediastinitis

Clinical

Signs/symptoms: localized pain (90%), fever (52%, with fever spikes and chills being rare), weight loss, paraspinal muscle spasm, radicular symptoms (50-93%) or myelopathy. VO sometimes produces few systemic effects (e.g. WBC and/or ESR may be normal). ≈ 17% of patients with VO have neurologic symptoms. The risk of paralysis may be higher in the older patient, in cervical VO (vs. thoracic or lumbar), in those with DM or rheumatoid arthritis, and in those with VO due to *S. aureus*[196]. Neurologic findings are uncommon initially, which may delay the diagnosis[204]. Sensory involvement is less common than motor and long-tract signs because compression is primarily anterior.

Pathogenesis

Source of infection

Sources of spontaneous VO: UTI (the most common), respiratory tract, soft-tissues (e.g. skin boils, IV drug abuse…), dental flora, blunt trauma to the spine. In 37% of cases a source is never identified[205].

Potential routes of spread

Three main routes (arterial, venous, and direct extension):

1. hematogenous: hematogenously disseminated spondylodiscitis in adults usually involves bone initially, and once infection is established in the subchondral space, spread is to the adjacent disc and thence to the next

VB[206]

A. arterial

B. via spinal epidural venous plexus (Batson's plexus[207])

2. direct extension (e.g. following surgery/LP, trauma, or local infection)

Organisms

1. *Staphylococcus aureus is* the most common pathogen (> 50%) as in SEA
2. *E. coli* is a distant second
3. organisms associated with some primary infection sites[208]:
   A. IV drug abusers: *Pseudomonas aeruginosa* is common
   B. urinary tract infections: *E. coli* & *Proteus spp.* are common
   C. respiratory tract infections: *Streptococcus pneumoniae*
   D. alcohol abuse: *Klebsiella pneumoniae*
   E. endocarditis:
      1. acute endocarditis: *Staph. aureus*
      2. subacute endocarditis: *Streptococcus spp.*
4. tuberculous VO: *Mycobacterium tuberculosis* (*see below*)
5. unusual organisms include: nocardia (*see page 356*)
6. *Mycobacterium avium complex (M. Avium* and *M. intracellulare*) **(MAC)** can cause pulmonary disease in nonimmunocompromised patients (usually elderly or on chronic steroids), but can cause VO similar to TB[209] as part of disseminated disease which usually occurs in HIV patients
7. rarely (< 2.5%) pyogenic infections are polymicrobial

Tuberculous vertebral osteomyelitis: AKA tuberculous spondylitis, AKA **Pott's disease**. More common in third world countries. Typically symptomatic for many months. Usually affects more than one level. The most common levels involved are the lower thoracic and upper lumbar levels. Has a predilection for the vertebral body, sparing the posterior elements. Psoas abscess is common (the psoas major muscle attaches to the bodies and intervertebral discs from T12-L5). Sclerosis of the involved vertebral body may occur. Definitive diagnosis requires the identification of acid fast bacilli on culture or Gram stain of biopsy material (may be done percutaneously).

Neurologic deficit develops in 10-47% of patients[210], and may be due to medullary and radicular inflammation in most cases. The infection itself rarely extends into the spinal canal[211], however, epidural granulation tissue or fibrosis or a kyphotic bony deformity may cause cord compression[210].

The role of surgical debridement and fusion with TB is controversial, and good results may be obtained with either medical treatment or surgery. Surgery may be more appropriate when definite cord compression is documented or for complications such as abscess or sinus formation[212].

DIAGNOSTIC TESTS

Laboratories

WBC: elevated in only ≈35% (rarely > 12,000), associated with poor prognosis.

ESR: elevated in almost all. Usually > 40 mm/hr. Mean: 85.

CRP: may be more sensitive than ESR, and may tend to normalize more quickly with appropriate treatment[213]. For normal values *see page 387*.

Cultures/biopsy

Culture: blood (positive in ≈ 50%), urine and any focal suppurative process.

Needle biopsy with cultures: can usually be done percutaneously via transpedicular approach with CT or fluoroscopic guidance. May be helpful even if blood cultures are positive (different organisms retrieved in 15%[214]) ∴ an attempt at direct culture from the involved site should be made. Ideally, cultures should be done before antibiotics are started. The yield of needle biopsy cultures ranges from 60-90%. Open biopsy is more sensitive, but morbidity is higher.

IMAGING

A comparison of sensitivities and specificities of various imaging modalities is shown in *Table 16-19*. NB: MRI and CT may be negative if done too early in the course.

MRI: T1WI → confluent low signal in vertebral bodies and intervertebral disc space. T2WI → increased intensity of involved VBs and disc space[215]. Contrast: enhancement of VB and disc, also look for paraspinal and epidural mass.

Plain x-ray: changes take from 2-8 weeks from the onset of infection to develop. Earliest changes are loss of cortical endplate margins and loss of disc space height.

Bone scan: three phase bone scan (*see page 140*) has reasonably good sensitivity and specificity. Gallium scan (*see page 141*) has better accuracy, findings include increased uptake in the 2 adjacent VBs with loss of intervening

disc[216]. Indium-111 labeled WBC scan: low sensitivity for vertebral osteomyelitis.

Table 16-19 Accuracy of various imaging modalities for vertebral osteomyelitis[215]

Modality	Sensitivity	Specificity	Accuracy
plain x-rays	82%	57%	73%
bone scan	90%	78%	86%
gallium scan	92%	100%	93%
bone scan + gallium scan	90%	100%	94%
MRI	96%	92%	94%

Work-up

In patients with suspected vertebral osteomyelitis (VO) (see text above for details):

1. clinical: history of IV drug abuse, DM, skin boil
2. physical exam: R/O radiculopathy & myelopathy, point tenderness over spine
3. diagnostic tests:
   A. bloodwork: WBC, ESR (a normal ESR is almost incompatible with VO), blood cultures
   B. imaging: MRI without and with contrast. Bone scan is used when suspicion is high and MRI is contraindicated
   C. percutaneous needle biopsy with cultures: usually by radiologist. Cultures should include: fungal, aerobic and anaerobic bacterial, and TB

Table 16-20 Candidates for non-surgical treatment in pyogenic spontaneous spondylodiscitis[208]

• organism identified
• antibiotic sensitivity
• single disc space involvement with little VB involvement
• minimal or no neurologic deficit
• minimal or no spinal instability

Treatment

90% of cases can be managed non-surgically with antibiotics and immobilization. Characteristics of potential candidates for non-surgical treatment are listed in *Table 16-20*. Must also take into account level(s) involved

and patient's condition.

In cases with high suspicion for VO, antibiotics may be started as soon as biopsy has been performed (some treat even earlier). For details of antimicrobials, see *Treatment*, page 379 (under spinal epidural abscess).

Improvement on imaging can lag behind clinical response and ESR/CRP.

Indications for neurosurgical[A] intervention:

1. progression of disease despite adequate best-case antibiotic therapy
2. spinal instability
3. spinal epidural abscess: *see* *page 376*
4. chronic infection refractory to medical management

For patients not being treated surgically:

1. percutaneous biopsy to obtain ID & sensitivity of organism
2. antibiotics:
   A. IV antibiotics for at least **6 weeks**[B] (longer, e.g. 12 weeks, if ESR not normalizing or if extensive bone involvement and paravertebral infection)
   B. followed by 6-8 weeks of oral agents[208]
3. pain medication as appropriate for pain
4. TLSO brace: to reduce pain (due to movement at involved site) and to reduce stress on weakened bone until healing
5. check upright films in the TLSO to verify stability in the brace
6. follow-up at approximately 8 and 12 weeks with x-rays in brace, then consider discontinuing brace if infection and pain are under control

Surgical treatment

Decompression of neural elements, removal of inflammatory tissue and infected bone to decrease bioburden. Use of instrumented fusion is not contraindicated even for pyogenic infections. Use of bone morphogenic protein (rhBMP-2) in 14 patients undergoing circumferential fusion for refractory infections did not produce complications[217].

16.15.3. Discitis

An uncommon primary infection of the nucleus pulposus. May start in cartilaginous endplate and spread to disc and vertebral body **(VB)**. Can occur following a number of procedures (see *Epidemiology*, page 386) or may be

"spontaneous" (the latter being more common). Often a benign, self-limited disease. Similar to vertebral osteomyelitis, except osteomyelitis primarily involves the VB and spreads secondarily to the disc space. Features and management common to spontaneous and postoperative discitis are discussed in the "general" section below, followed by sections describing characteristics unique to each (see *Spontaneous discitis*, page 386 or *Postoperative discitis* on page 386).

Many radiographic features of spondylodiscitis and tumor (metastatic and primary) are similar, but tumors rarely involve the disc space, whereas most infections begin in, or before too long, involve the disc space (for more details, see *Differentiating factors*, page 1233).

DISCITIS IN GENERAL

CLINICAL

1. symptoms:
   A. pain (the primary symptom)
      1. local pain, moderate to severe, exacerbated by virtually any motion of the spine, usually well localized to the level of involvement
      2. radiating to abdomen[218], hip, leg, scrotum, groin, or perineum
      3. radicular symptoms: in 50%[219] to 93%[220] depending on the series
   B. fever and chills (only 30-50% are febrile)
2. signs:
   A. tenderness
   B. paravertebral muscle spasm
   C. limitation of movement

A. intervention by a general surgeon may be indicated for empyema, psoas abscess…

B. the rate of treatment failure is increased when IV antibiotics are given for < 4 weeks[208]

WORK-UP (SEE TEXT FOR DETAILS)

1. MRI: also evaluates for epidural spread
2. blood tests
   A. WBC

B. ESR & CRP

C. blood cultures

3. echocardiogram: rule-out endocarditis or valvular vegetations
4. percutaneous needle biopsy

RADIOGRAPHIC EVALUATION

A characteristic radiographic finding that helps distinguish infection from meta-static disease is that destruction of the disc space is highly suggestive of infection, whereas in general, tumor does not cross the disc space (see *Differentiating factors*, page 1233).

PLAIN X-RAYS

Usually not helpful for early diagnosis. Sequence of changes on plain films:

- earliest changes: interspace narrowing with some demineralization of the VB. Not seen < 2-4 wks following onset of clinical symptoms, nor later than 8 wks
- sclerosis (eburnation) of adjacent cortical margins with increased density of adjacent areas of VB representing new bone formation, starting 4-12 weeks following onset of clinical symptoms
- irregularity of the adjacent vertebral endplates, with sparing of the pedicles (except for tuberculosis, which may involve the pedicles)
- in 50% of cases, the infection remains confined to the disc space, in the other 50% it spreads to adjacent VB
- a late finding is widening (ballooning) of the disc space with erosion of the VB
- circumferential bone formation may lead to exuberant spur formation between VBs 6-8 months into course of illness
- spontaneous fusion of the VB may occur

MRI

Demonstrates involvement of disc space and of VBs. MRI can R/O paravertebral or epidural spinal abscess but is poor in assessing bony fusion. As sensitive as radionuclide bone scan. Characteristic finding: decreased signal from the disc and adjacent portion of VBs on T1WI, and increased signal from these structures on T2WI. Characteristic findings may occur 3-5 days after onset of symptoms. MRI also rules-out other causes of postop pain (epidural abscess, recurrent/residual disc herniation…).

The triad of gadolinium enhancement shown in *Table 16-21* is strongly suggestive of discitis (some asymptomatic patients may have some of these

findings, but they rarely have all)[221].

Table 16-21 Gadolinium enhancement in discitis

Location of gadolinium enhancement	Number (out of 15 patients without discitis)	Number (out of 7 patients with discitis)
1. vertebral bone marrow	1	7
2. disc space	3	5
3. posterior annulus fibrosus	13	7

CT

May also R/O paravertebral or epidural spinal abscess, and is better for assessing bony fusion. With the addition of water soluble intrathecal contrast, also assesses the spinal canal for compromise.

Diagnostic criteria

Three basic changes on CT[222] (if all 3 are present, pathognomonic for discitis; if only the 1st 2 are present, then only 87% specific for discitis):

1. endplate fragmentation
2. paravertebral soft-tissue swelling with obliteration of fat planes
3. paravertebral abscess

Spine polytomograms

For postoperative discitis **(POD)**: performed through level of previous discectomy. Otherwise, center tomograms on painful level.

Scintigrams

Very sensitive for discitis and vertebral osteomyelitis (85% sensitivity), but may be negative in up to 85% of patients with Pott's disease. Uses either technetium-99 (abnormal as early as 7 days following onset of clinical symptoms) or gallium-67 (abnormal within 14 days). A positive scan shows focal increased uptake in adjacent endplates, and may be differentiated from osteomyelitis which will involve only one endplate. A positive scan is not specific for infection, and may also occur with neoplasms, fractures, and degenerative changes.

Laboratory studies

ESR: In non-immunocompromised patients, ESR will be elevated in almost all

cases with an average of 60 mm/hr (although it can rarely occur, a normal ESR should call the diagnosis into question). Interpreting ESR may be more problematic in post-op discitis (*see page 387*). ESR may be useful to follow as an indicator of response to treatment.

C-reactive protein: *See C-reactive protein* on page 387.

WBC: Peripheral WBC is often normal, and rarely is elevated above 12,000.

PPD: Applied to help R/O Pott's disease (see *Tuberculous vertebral osteomyelitis*, page 381), may be negative in 14% of cases[223].

Cultures: An attempt should be made to obtain direct cultures from the involved disc space. These may be obtained percutaneously with CT or other radiographic guidance (reported up to 60% positive culture rate; if available, a nucleotome provides a higher yield than e.g. Craig needle biopsy), or from intraoperative specimen (NB: surgery for open biopsy alone is usually not indicated). Staining for TB must be done in all cases.

Blood cultures may be positive in ≈ 50% of cases, and are helpful in guiding choice of antimicrobial agent when positive.

PATHOGENS

Staphylococcus aureus is the most common organism when direct cultures are obtained, followed by *S. albus* and *S. epidermidis* (*S. epidermidis* is the most common pathogen in POD). Gram negative organisms may also be found, including *E. coli* and Proteus species. Enteric flora in post-op discitis may due to undetected breach of the anterior longitudinal ligament with bowel perforation.

Pseudomonas aeruginosa may be more common in IV drug abusers.

H. flu is common in juvenile discitis (*see below*).

Tuberculous spondylitis (Pott's disease) may also occur.

TREATMENT

Outcome is generally good, and antibiotics together with immobilization are adequate treatment in ≈ 75% of cases. Occasionally surgery is required. Also see *Management*, page 387 under postoperative discitis for other aspects of management.

IMMOBILIZATION

Probably does not affect final outcome, but generally affords earlier pain relief, and may allow return to activity at an earlier time.

Most patients are started on strict bed rest, and are fitted for a plastic-type body jacket in which they are allowed to ambulate, and in which they remain for 6-8 weeks on the average. Alternative forms of immobilization include spica cast (provides better immobilization) and a corset-type brace.

ANTIBIOTICS

Current thinking is that most patients should receive antibiotics, guided by the results of the direct cultures when positive. In the 40-50% of cases where no organism is isolated, broad spectrum antibiotics should be used.

Two alternative treatment plans suggested:

1. treat with IV antibiotics for an arbitrary period of time, usually ≈ 4-6 weeks, followed with oral antibiotics for an additional 4-6 weeks
2. treat with IV antibiotics until the ESR normalizes, then change to PO

SURGERY

Required in only ≈ 25% of cases. Debridement may be done through the previous laminectomy site. However, if there has been significant bone loss and instability, then an anterior discectomy and fusion through a retroperitoneal approach may be required.

Surgery is reserved for:

1. situations where the diagnosis is uncertain, especially when neoplasm is a strong consideration (CT guided needle biopsy may help here)
2. decompression of neural structures, especially with associated spinal epidural abscess or compression by reactive granulation tissue. Ascending numbness, weakness, or onset of neurogenic bladder herald cauda equina syndrome
3. drainage of associated abscess, especially septated abscesses that might be recalcitrant to CT guided percutaneous needling
4. rarely, to fuse an unstable spine. Poorly endorsed in the face of active infection, especially since most go on to spontaneous fusion

Approaches

1. anterior discectomy and corpectomy removes the offending infected tissue, with strut graft using iliac crest (or, in the thoracic region, a posterolateral approach, with the strut made from the resected rib if large enough)

2. posterior laminectomy may be adequate for emergent decompression, but does not allow access to the site of pathology in cervical or thoracic regions

SPONTANEOUS DISCITIS

No recent history of surgery or instrumentation. Higher incidence of neurologic deficits and radiculopathy than with postoperative discitis **(POD)**.

Two distinct types:

1. juvenile: more common; age usually < 20 yrs (*see below*)
2. adult: usually occurs in susceptible patients (diabetics, IV drug abusers)

JUVENILE DISCITIS

Age usually < 20 yrs, with a peak between 2-3 years. Probably due to the presence of primordial feeding arteries that nourish the nucleus pulposus and which involute at ≈ 20-30 yrs age. Lumbar spine is more commonly involved than thoracic or cervical. Common presentation: refusal to walk or stand progressing to refusal to sit in young children. Back pain is most common in children > 9 yrs age. Low grade fever may be present. ESR is usually 2-3 **x** normal. WBC is sometimes elevated. *H. flu* is a more commonly seen pathogen in this group.

In most cases, there is complete resolution in 9-22 weeks without recurrence in long-term follow-up studies[210 (p 365-71)]. Surgery is reserved for the rare case that progresses in spite of antibiotics, for spinal instability, or for recurrent cases.

Most authors reserve antibiotics for patients with[210 (p 365-71)]:

1. positive cultures (blood cultures or biopsy cultures)
2. elevated WBC count, constitutional symptoms, or high fever
3. poor response to rest or immobilization
4. neurologic sequelae (very rare)

Antibiotics should be given for a total of 4-6 weeks. Start with IV antibiotics, and when clinical symptoms improve convert to PO for the remainder of therapy.

POSTOPERATIVE DISCITIS

Unless otherwise specified, the following is based on a series of 27 post-op cases identified retrospectively at Duke[224].

Epidemiology

Incidence after lumbar discectomy[225]: 0.2-4% (realistic estimate is probably at the lower end of this range). May also occur after LP, myelogram, cervical laminectomy, lumbar sympathectomy, chemonucleolysis[226], discography (*see page 436*), fusions and other procedures. Very rare after ACDF. Risk factors include: advanced age, obesity, immuno-suppression, systemic infection at the time of surgery.

Pathophysiology

There is some controversy as to whether some cases of post-op discitis are not infectious[227], an autoimmune process has been implicated in some of these so-called "avascular" or "chemical" or "aseptic" discitis cases. These cases are less common than infectious ones. ESR and CRP abnormalities may be less pronounced in these patients, and biopsy of the disc space fails to grow organisms or show signs of infection (infiltrates of lymphocytes or PMNS) on microscopy[227].

In septic cases, various mechanisms for infection have been proposed: direct inoculation at the time of surgery, infection following aseptic necrosis of disc material…

Clinical

1. interval from operation to onset of symptoms: 3 days to 8 mos (most commonly 1-4 wks post-op, usually after an initial period of pain relief and recovery from surgery). 80% present by 3 wks
2. symptoms:
   A. moderate to (usually) severe back pain at the site of operation was the most common symptom, exacerbated by virtually any motion of the spine, often accompanied by paraspinal muscle spasms. Back pain is usually out of pro-portion to the findings
   B. fever (> 38° C in 9 patients; literature reports only 30-50% are febrile) and chills
   C. pain radiating to hip, leg, scrotum, groin, abdomen or perineum (true sciatica is uncommon)
3. signs: all had paravertebral muscle spasm and limited range of motion of the spine. 13 were virtually immobilized by pain. Point tenderness over infected spine occurred in 9, expressible pus in 2 (literature reports 0-8%). No new neurologic deficits were noted. Only 10-12% have associated

wound infection[219]

4. lab findings:
   - ESR: 26/27 had ESR > 20 mm/hr (60 = ave.; > 40 in 17 patients; > 100 in 5 patients; the single patient < 20 was on steroids). ESR increases after un-complicated discectomy, peaking at 2-5 days, and can fluctuate for 3-6 weeks before normalizing[228]. A n elevated ESR that never decreases after surgery is a strong indicator of discitis. NB: ESR in anemic patients is un-reliable and no reference range can be established (use CRP in these cases)
   - C-reactive protein **(CRP)**[228]: an acute phase protein synthesized by hepatocytes that because of rapid decomposition may be a more specific indicator of post-op infection than ESR. Values vary from lab to lab, but CRP is normally not detectable in the blood (i.e. < 0.6 mg/dL = 6 mg/L). After uncomplicated discectomy (i.e. in the absence of discitis), CRP peaks ≈ 2-3 days post-op (to 4.6 ± 2.1 mg/dL after lumbar microdiscectomy, 9.2 ± 4.7 after conventional lumbar discectomy, 7.0 ± 2.3 after anterior lumbar fusion, and 17.3 ± 3.9 after PLIF), and returns to normal between 5-14 days post op
   - WBC: elevated > 10,000 in only 8/27 (prevalence in literature: 18-30%)

Radiographic evaluation

Also, see *Radiographic evaluation*, page 384 under *Discitis in general*.

In postoperative discitis **(POD)**, the average time from surgery to changes on plain x-ray is 3 mos (range: 1-8 mos). Changes are detectable earlier on polytomograms (3 wks to 2 mos). Average time from first change to spinal fusion: 2 yrs.

Pathogens

See Table 16-22. Most studies report *S. aureus* as the most commonly identified organism, accounting for ≈ 60% of positive cultures[225], followed by other staph species. Also reported: Gram-negative organisms (including *E. coli*), *Strep viridans*, *Streptococcus species* anaerobes, TB and fungi.

Blood cultures were positive in 2 of 6 (both *S. aureus*).

For culture techniques, *see below*.

Table 16-22 Culture results (14 patients, Craig needle biopsy)

Organism	No. of patients
Staphylococcus epidermidis	4

S. aureus	3
No growth	7

MANAGEMENT

1. admitting labs (in addition to routine): ESR, C-reactive protein, CBC, blood cultures
2. analgesics + muscle relaxants (e.g. diazepam (Valium®) 10 mg PO TID)
3. antibiotics:
   - IV antibiotics for 1-6 wks (or until ESR decreases), then PO for 1-6 mos (typically 6 weeks)
   - most start with anti-staphylococcal antibiotics (initial empiric therapy: vancomycin + PO rifampin) and a broad spectrum antibiotic (e.g. Cefizox), modify based on sensitivities if positive cultures are obtained
4. activity restriction (one of the following used, usually until significant pain relief):
   - spinal immobilization with spica cast or plastic body jacket
   - strict bed rest
   - activity with corset
5. some authors recommend steroid therapy initially to assist pain relief
6. cultures: performed if radiographs suspicious, usually performed utilizing percutaneous CT-guided technique
   A. sites
      1. disc aspiration if evidence of disc space involvement
      2. needling of paraspinal mass if present
   B. send cultures for the following:
      1. stains
         a. Gram stain
         b. fungal stain
         c. AFB stain
      2. culture
         a. routine cultures: aerobic and anaerobic
         b. fungal culture: this is not only helpful for fungus, but since these cultures are kept for longer period and any growth that occurs will be further characterized, fastidious or indolent bacterial organisms may sometimes be identified
         c. TB culture
7. 3 patients in Duke series underwent anterior discectomy and fusion after

unsuccessful medical therapy

OUTCOME

9 patients developed bony bridging in 12-18 mos; 10 developed bony fusion in 18-24 mos.

All patients eventually become pain free (or significantly improve). This is not the case in all series, where some report 60% were pain free at F/U, others found slight back pain in most patients, and yet others report severe chronic LBP in 75%[225]. 67-88% return to their previous work, and 12-25% received disability pension; these numbers are similar to the outcome from disc surgery in general.

No difference in outcome was found for the various activity restrictions specified, except for earlier pain relief with first two types listed above.

16.16. References

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17. Seizures

17.1. Seizure classification

Definition of a seizure: an abnormal paroxysmal cerebral neuronal discharge that results in alteration of sensation, motor function, behavior or consciousness. Seizures may be classified by type, etiology, and by epileptic syndromes.

Classification of major seizure types[1-3]

1. primary **generalized**: bilaterally symmetrical and synchronous involving both cerebral hemispheres at the onset, no local onset, consciousness lost from the start. Represents ≈ 40% of all seizures
   A. generalized tonic-clonic **(GTC)** (née: grand-mal seizure): generalized seizure that evolves from tonic to clonic motor activity. This is a specific type and does <u>NOT</u> include partial seizures that generalize secondarily
   B. clonic seizures: fairly symmetric, bilateral synchronous semirhythmic jerking of the UE & LE, usually with elbow flexion and knee extension
   C. tonic seizures: sudden sustained increased tone with a characteristic guttural cry or grunt as air is forced through adducted vocal cords
   D. **absence** (née: petit-mal seizure): impaired consciousness with mild or no motor involvement (*see below*)
      1. typical absences
      2. atypical absences: more heterogeneous with more variable EEG pattern then typical absence. Seizures may last longer
   E. myoclonic seizures: shock-like body jerks (1 or more in succession) with generalized EEG discharges
   F. atonic seizures (AKA astatic seizures or “drop attacks”): sudden brief loss of tone that may cause falls
2. **partial** (née focal seizure): implies one hemisphere involved at onset. About 57% of all seizures. A new onset of partial seizure represents a

structural lesion until proven otherwise

A. simple partial seizure (no impairment of consciousness)
    1. with motor signs (including Jacksonian)
    2. with sensory symptoms (special sensory or somatosensory)
    3. with autonomic signs or symptoms
    4. with psychic symptoms (disturbance of higher cerebral function)

B. complex partial seizure (many used to be classified as psychomotor seizure, often attributed to temporal lobe but they can arise from any cortical area): any alteration of consciousness, usually LOC or automatisms (including lip smacking, chewing, or picking with the fingers) with autonomic aura (usually an epigastric rising sensation)
    1. simple partial onset followed by impairment of consciousness (may have premonitory **aura**)
        a. without automatisms
        b. with automatisms
    2. with impairment of consciousness at onset
        a. without automatisms (impairment of consciousness only)
        b. with automatisms

C. partial seizure with secondary generalization
    1. simple partial evolving to generalized
    2. complex partial evolving to generalized
    3. simple partial evolving to complex partial evolving to generalized

3. unclassified epileptic seizures: ≈ 3% of all seizures

Classification by etiology (and some epileptic syndromes)

This list is not all inclusive (see reference[2, 3]).

1. **symptomatic** (AKA “secondary”): seizures of known etiology (e.g. CVA, tumor…)
    A. temporal lobe epilepsies:
        1. mesial temporal sclerosis: *see below*
2. **idiopathic** (AKA “primary”): no underlying cause. Includes:
    A. juvenile myoclonic epilepsy: *see below*
3. **cryptogenic**: seizures presumed to be symptomatic but with unknown etiology
    A. West syndrome (infantile spasms, Blitz-Nick-Salaam Krämpfe): *see below*

B. Lennox-Gastaut syndrome: *see below*

4. special syndromes: situation-related seizures

A. febrile seizures: *see page 402*

B. seizures occurring only with acute metabolic or toxic event: e.g. alcohol

KEY distinctions (having therapeutic implications)

In generalized tonic-clonic seizures: primary generalized vs. partial with secondary generalization (often, local onset may not be observed).

In staring spells: absence vs. complex partial.

Epilepsy

A disorder, not a single disease. Characterized by recurrent (2 or more), unprovoked seizures.

Absence seizure

Formerly called petit-mal seizure. Impaired consciousness with mild or no motor involvement (automatisms occur more commonly with bursts lasting > 7 secs). No post-ictal confusion. Aura rare. May be induced by hyperventilation **x** 2-3 mins. EEG shows **spike and wave** at exactly 3 per second.

Uncinate seizures

Obsolete term: "uncal fits". Seizures originating in the inferior medial temporal lobe, usually in the hippocampal region. May produce olfactory hallucinations (kakosmia or cacosmia: the perception of bad odors where none exist).

Mesial temporal sclerosis[4, 5]

The most common cause of intractable temporal lobe epilepsy. Specific pathologic basis: hippocampal sclerosis (cell loss in hippocampus on one side). Characteristics are shown in *Table 17-1*. For differential diagnosis, *see page 1228*.

Adult seizures are initially responsive to medical therapy but become more varied and refractory, and may respond to seizure surgery.

Juvenile myoclonic epilepsy[7]

Sometimes called bilateral myoclonus. 5-10% of cases of epilepsy. An

idiopathic generalized epilepsy syndrome with age-related onset consisting of 3 seizure types:

1. myoclonic jerks: predominantly after waking
2. generalized tonic-clonic seizures
3. absence

Table 17-1 Syndrome of mesial temporal-lobe epilepsy[6]

History
• higher incidence of complicated febrile seizures than in other types of epilepsy
• common family history of epilepsy
• onset in latter half of first decade of life
• auras in isolation are common
• infrequent secondarily generalized seizures
• seizures often remit for several years until adolescence or early adulthood
• seizures often become medically refractory
• common interictal behavioral disturbances (especially depression)
Clinical features of seizures
• most have aura (especially epigastric, emotional, olfactory or gustatory) **x** several secs
• CPS often begin with arrest & stare; oroalimentary & complex automatisms are common. Posturing of contralateral arm may occur. Seizure usually lasts 1-2 mins
• postictal disorientation, recent-memory deficit, amnesia of ictus and (in dominant hemisphere) aphasia usually lasts several mins
Neurologic and laboratory features
• neuro exam: normal except memory deficit
• MRI: hippocampal atrophy and signal alteration with ipsilateral dilatation of temporal horn of lateral ventricle
• unilateral or bilateral independent anterior temporal EEG spikes with maximal amplitude in basal electrodes
• external ictal EEG activity only with CPS, usually initial or delayed focal rhythmic onset pattern of 5-7 Hz, maximal in 1 basal temporal derivation
• interictal fluorodeoxyglucose PET scan: hypometabolism in temporal lobe and possibly ipsilateral thalamus and basal ganglia
• neuropsychological testing: memory dysfunction specific to involved temporal lobe
• Wada test: amnesia with contralateral amobarbital injection (*see page 421*)

EEG → polyspike discharges. Strong family history (some studies showing linkage to the HLA region on the short arm of chromosome 6). Most responsive to depakene.

WEST SYNDROME

This term is being used less frequently as it appears not to be a homogeneous group. Classically a seizure disorder that usually appears in first year of life, and consists of recurrent, gross flexion and occasionally extension of the trunk and limbs (massive myoclonus, AKA infantile spasms, AKA salaam seizures, AKA jackknife spasms). Seizures tend to diminish with age, often abating by 5 yrs. Usually associated with mental retardation. 50% may develop complex-partial seizures, some of the rest may develop Lennox-Gastaut syndrome (*see below*).

An associated brain lesion may be found in some.

EEG → the majority show either interictal **hypsarrhythmia** (huge spike/wave plus slow wave resembling muscle artifact) or modified hypsarrhythmia at some point.

Usually dramatic response of seizures and EEG findings to ACTH or corticosteroids.

LENNOX-GASTAUT SYNDROME

Rare condition that begins in childhood as atonic seizures ("drop attacks"). Often develops into tonic seizures with mental retardation. Seizures are often polymorphic, difficult to treat medically, and may occur as often as 50 per day. May also present with status epilepticus. Approximately 50% of patients have reduced seizures with valproic acid. Corpus callosotomy may reduce the number of atonic seizures.

TODD'S PARALYSIS

A post-ictal phenomena in which there is partial or total paralysis usually in areas involved in a partial seizure. More common in patients with structural lesions as the source of the seizure. The paralysis usually resolves slowly over a period of an hour or so. Thought to be due to depletion of neurons in the wake of the extensive electrical discharges of a seizure. Other similar phenomena include post-ictal aphasia and hemianopsia.

17.1.1. Factors that lower the seizure threshold

Factors that lower the seizure threshold (i.e. make it easier to provoke a seizure) in individuals with or without a prior seizure history include many items listed under *Etiologies* of *New onset seizures* (*see below*) as well as:

1. sleep deprivation
2. hyperventilation
3. photic stimulation (in some)
4. infection: systemic (febrile seizures, *see page 402*), CNS…
5. metabolic disturbances: electrolyte imbalance (especially profound hypoglycemia), pH disturbance (especially alkalosis), drugs… (*see below*)
6. head trauma: closed head injury, penetrating trauma (*see page 398*)
7. cerebral ischemia: CVA (*see below*)
8. "kindling": a concept that repeated seizures may facilitate the

development of later seizures

17.2. Special types of seizures

17.2.1. New onset seizures

The age adjusted incidence of new onset seizures in Rochester, Minnesota was 44 per 100,000 person years[8].

Etiologies: In patients presenting with a first-time seizure, etiologies include (modified[9]):

1. following neurologic insult: either acutely (i.e. < 1 week) or remotely (> 1 week, and usually < 3 mos from insult)
   A. cerebrovascular accident (CVA, or stroke): 4.2% had a seizure within 14 days of a CVA. Risk increased with severity of stroke[10]
   B. head trauma: closed head injury, penetrating trauma (*see page 398*)
   C. CNS infection: meningitis, cerebral abscess, subdural empyema
   D. febrile seizures: *see page 402*
   E. birth asphyxia
2. underlying CNS abnormality
   A. congenital CNS abnormalities
   B. degenerative CNS disease
   C. CNS tumor: metastatic or primary
   D. hydrocephalus
   E. AVM
3. acute systemic metabolic disturbance
   A. electrolyte disorders: uremia, hyponatremia, hypoglycemia (especially profound hypoglycemia), hypercalcemia
   B. drug related, including:
      1. alcohol-withdrawal: *see page 399*
      2. cocaine toxicity: *see page 276*
      3. opioids (narcotics), principally associated with the following:
         a. propoxyphene (Darvon®)
         b. meperidine (Demerol®): may also cause delerium
         c. the street drug combination “T’s and blues” (pentazocine

(Talwin®) + the antihistamine tripelennamine)
4. phenothiazine antiemetics
5. with administration of flumazenil (Romazicon®) to treat benzodiazepine **(BDZ)** overdose (especially when BDZs are taken with other seizure lowering drugs such as tricyclic antidepressants or cocaine
6. phencyclidine **(PCP)**: originally used as an animal tranquilizer
7. cyclosporine: can affect Mg^{++} levels

C. eclampsia

4. idiopathic

In 166 pediatric patients presenting to an emergency department with either a chief complaint of, or a discharge diagnosis of a first-time seizure[11]:

1. 110 were found to actually have either a recurrent seizure or a nonictal event
2. of the 56 patients actually thought to have had a first-time seizure
   A. 71% were febrile seizures
   B. 21% were idiopathic
   C. 7% were "symptomatic" (hyponatremia, meningitis, drug intoxication…)

In a prospective study of 244 patients with a new-onset unprovoked seizure, only 27% had further seizures during follow-up[9, 12]. Recurrent seizures were more common in patients with a family seizure history, spike-and-waves on EEG, or a history of a CNS insult (CVA, head injury…). No patient seizure-free for 3 years had a recurrence. Following a second seizure, the risk of further seizures was high.

EVALUATION

Adults

A new-onset seizure in an adult in the absence of obvious cause (e.g. alcohol withdrawal) should prompt a search for an underlying basis (the onset of idiopathic seizures, i.e. epilepsy, is most common before or during adolescence). A CT or MRI (without and with enhancement) should be performed. A systemic work-up should be done to identify the presence of any factors listed previously (*see above*). If all this is negative, then an MRI should be performed if not already done. If this is negative also, a repeat study (CT or MRI) should be done

in ≈ 6 months and at 1 and possibly 2 years to rule-out a tumor which might not be evident on the initial study.

Pediatrics

Among pediatric patients with first-time seizures, laboratory and radiologic evaluations were often costly and not helpful[11]. A detailed history and physical exam were more helpful.

Management

Management of an adult with the new onset of idiopathic seizures (i.e. no abnormality found on CT or MRI, no evidence of drug withdrawal) is controversial. In one study, an EEG was performed, which if normal was followed by a sleep deprived EEG with the following observations[13]:

1. there is substantial interobserver variation in interpreting such EEGs
2. if both EEGs were normal, the 2-yr recurrence rate of seizures was 12%
3. if one or both EEGs showed epileptic discharges, the 2-yr recurrence rate was 83%
4. the presence of nonepileptic abnormalities in one or both EEGs had a 41% 2-yr recurrence rate
5. the recurrence rate with focal epileptic discharges (87%) was slightly higher than for generalized epileptic discharges (78%)

The conclusion is that EEGs thus obtained have moderate predictive value, and may be factored into the decision of whether or not to treat such seizures with AEDs.

17.2.2. Posttraumatic seizures

Key concepts:

- 2 categories: early (≤ 7 days) and late (> 7 days) after head trauma
- anticonvulsants **(AEDs)** may be used to prevent early posttraumatic seizures **(PTS)** in patients at high risk for seizures (*see text*)
- prophylactic AEDs do NOT reduce the frequency of late PTS
- discontinue AEDs after 1 week except for cases meeting specific criteria (*see text*)

Posttraumatic seizures **(PTS)** are often divided (arbitrarily) into: early (occurring within 1 week of injury) and late (thereafter)[14]. There may be justification for a third category: "immediate", i.e. within minutes to an hour or so.

Early PTS (≤ 7 days after head trauma)

30% incidence in severe head injury ("severe" defined as: LOC > 24 hrs, amnesia > 24 hrs, focal neuro deficit, documented contusion, or intracranial hematoma) and ≈ 1% in mild to moderate injuries. Occurs in 2.6% of children < 15 yrs age with head injury causing at least brief LOC or amnesia[15].

Early PTS may precipitate adverse events as a result of elevation of ICP, alterations in BP, changes in oxygenation, and excess neurotransmitter release[16].

Late onset PTS (> 7 days after head trauma)

Estimated incidence 10-13% within 2 yrs after "significant" head trauma (includes LOC > 2 mins, GCS < 8 on admission, epidural hematoma…) for all age groups[17, 18]. Relative risk: 3.6 times control population. Incidence in severe head injury >> moderate > mild[15].

The incidence of early PTS is higher in children than adults, but late seizures are much less frequent in children (in children who have PTS, 94.5% develop them within 24 hrs of the injury[19]). Most patients who have not had a seizure within 3 yrs of penetrating head injury will not develop seizures[20]. Risk of late PTS in children does not appear related to the occurrence of early PTS (in adults: only true for mild injuries). Risk of developing late PTS may be higher after repeated head injuries.

Penetrating trauma

The incidence of PTS is higher with penetrating head injuries than with closed head injuries (occurs in 50% of penetrating trauma cases followed 15 yrs[21]).

TREATMENT

A prospective double blind study of patients at high risk of PTS (excluding penetrating trauma) showed a 73% reduction of risk of early PTS by administering 20 mg/kg loading dose of PHT within 24 hrs of injury and maintaining high therapeutic levels; but after 1 week there was no benefit in

continuing the drug (based on intention to treat)[22]. Carbamazepine (Tegretol®) has also been shown to be effective in reducing the risk of early PTS, and valproic acid is currently being studied[16].

Phenytoin has adverse cognitive effects when given long-term as prophylaxis against PTS[23].

TREATMENT GUIDELINES

Based on available information (*see above*) it appears that:

1. no treatment studied effectively impedes epileptogenesis
2. in high-risk patients (*see Table 17-2*), AEDS reduces the incidence of early PTS
3. however, no study has shown that reducing early PTS improves outcome[24]
4. once epilepsy has developed, continued AEDs reduces the recurrence of seizures

The following are therefore offered as guidelines.

Initiation of AEDs

AEDs may be considered for short term use especially if a seizure could be detrimental[A]. Early posttraumatic seizures were effectively reduced when phenytoin was used for 2 weeks following head injury with no significant increased risk of adverse effects[25].

A. acutely, seizures may elevate ICP, and may adversely affect blood pressure and oxygen delivery, and may worsen other injuries (e.g. spinal cord injury in the setting of an unstable cervical spine)[16]

Option: begin AEDs (usually phenytoin or carbamazepine) within 24 hrs of injury in the presence of any of the high risk criteria shown in *Table 17-2* (modified[16, 19, 22, 26]). When using PHT, load with 20 mg/kg and maintain high therapeutic levels (*see page 409*). Switch to phenobarbital if PHT not tolerated.

Table 17-2 High risk criteria for PTS

1. acute subdural, epidural, or intracerebral hematoma
2. open-depressed skull fracture with parenchymal injury
3. seizure within the first 24 hrs after injury
4. Glasgow Coma Scale score < 10

5. penetrating brain injury
6. history of significant alcohol abuse
7. ± cortical (hemorrhagic) contusion on CT

Discontinuation of AEDs

1. taper AEDs after 1 week of therapy except in the following:
   A. penetrating brain injury
   B. development of late PTS (i.e. a seizure > 7 days following head trauma)
   C. prior seizure history
   D. patients undergoing craniotomy[27]
2. for patients not meeting the criteria to discontinue AEDs after 1 week (*see above*):
   A. maintain ≈ 6-12 mos of therapeutic AED levels
   B. recommend EEG to rule-out presence of a seizure focus before discontinuing AEDs (predictive value) for the following:
      1. repeated seizures
      2. presence of high risk criteria shown in *Table 17-2*.

17.2.3. Alcohol withdrawal seizures

Also, see *Alcohol withdrawal syndrome*, page 273. The withdrawal syndrome may begin hours after the EtOH peak (*see page 274* for prevention and treatment). Ethanol withdrawal seizures are classically seen in up to 33% of habituated drinkers within 7-30 hours of cessation or reduction of ethanol intake. They typically consist of 1-6 tonic-clonic generalized seizures without focality within a 6 hour period[28]. Seizures usually occur before delerium develops. They may also occur during intoxication (without withdrawal).

The seizure risk persists for 48 hrs (risk of delerium tremens **(DTs)** continues beyond that), thus a single loading dose of PHT is frequently adequate for prophylaxis. However, since most EtOH withdrawal seizures are single, brief, and self-limited, PHT has not been shown to be of benefit in uncomplicated cases and is thus usually not indicated. Chlordiazepoxide (Librium®) or other benzodiazepines administered during detoxification reduces the risk withdrawal seizures[29] (*see page 274*).

Evaluation

The following patients should have a CT scan of the brain, and should be admitted for further evaluation as well as for observation for additional seizures or for DTs:

1. those with their first EtOH withdrawal seizure
2. those with focal findings
3. those having more than 6 seizures in 6 hrs
4. those with evidence of trauma

Other causes of seizure should also be considered, e.g. a febrile patient may require an LP to R/O meningitis.

Treatment

A brief single seizure may not warrant treatment, except as outlined below. A seizure that continues beyond 3-4 minutes may be treated with diazepam or lorazepam, with further measures used as in status epilepticus (*see page 402*) if seizures persist. Loading with phenytoin (18 mg/kg = 1200 mg/70 kg, *see page 409*) and long-term treatment is indicated for:

1. a history of previous alcohol withdrawal seizures
2. recurrent seizures after admission
3. history of a prior seizure disorder unrelated to alcohol
4. presence of other risk factors for seizure (e.g. subdural hematoma)

17.2.4. Nonepileptic seizures

AKA pseudoseizures (some prefer not to use this term since it may connote voluntary feigning of seizures), with the term psychogenic seizures being preferred for nonepileptic seizures **(NES)** with a psychologic etiology (psychogenic seizures are real events and may not be under voluntary control)[30].

The hazard of NES is that patients may end up needlessly taking AEDs, which in some cases may worsen NES. Possible etiologies of NES are given in *Table 17-3*. Most NES are psychogenic.

DDx for seizures:

1. psychogenic: 20-90% of patients with intractable seizures referred to epilepsy centers. These patients carry the diagnosis of seizures from 5-7 years. Up to 50% of these may have legitimate seizures at some time as

well[31].

2. tic: can be suppressed, is not repetitive (if repetitive, may be hemifacial spasm)
3. movement disorder: myoclonus (can be epileptic or non-epileptic)
   A. cataplexy: e.g. with narcolepsy often provoked by laughter or other emotional stimulus (can rarely be caught on EEG, when it is it shows REM intrusion into wakefulness)
   B. parasomnia: a sleep movement disorder (occurs during sleep). Includes: night terrors (occurs in slow wave sleep, vs. nightmare which occurs in REM), sleep walking, REM behavior disorders (usually occurs in older men, and there is a high prob-ability they will go on to have degenerative brain disease (used to be called paroxysmal nocturnal PNT). Head banging is a benign parasomnia
4. syncope: 90% of the time people who faint have myoclonic jerks or shaking[32]
5. TIA

Table 17-3 Differential diagnosis of nonepileptic seizures[30]

1. psychologic disorders (psychogenic seizure) A. somatoform disorders: especially conversion disorder B. anxiety disorders: especially panic attack and posttraumatic stress disorder C. dissociative disorders D. psychotic disorders E. impulse control disorders F. attention-deficit disorders* G. factitious disorders: including Munchausen's syndrome
2. cardiovascular disorders A. syncope B. cardiac arrhythmias C. transient ischemic attacks D. breath-holding spells*
3. migraine syndromes A. complicated migraines* B. basilar migraines
4. movement disorders A. tremors B. dyskinesias C. tics*, spasms D. other (including shivering)
5. parasomnias & sleep-related disorders A. night terrors*, nightmares*, somnambulism* B. narcolepsy, cataplexy C. rapid eye movement behavior disorder D. nocturnal paroxysmal dystonia
6. gastrointestinal disorders A. episodic nausea or colic*

	B. cyclic vomiting syndrome*
7. other	
	A. malingering
	B. cognitive disorders with episodic behavioral or speech symptoms
	C. medication effects or toxicity
	D. daydreams*

* usually encountered in children

DIFFERENTIATING NES FROM EPILEPTIC SEIZURES

Distinguishing between epileptic seizures **(ES)** and NES is a common clinical dilemma. There are unusual seizures that may fool experts[33]. Some frontal lobe and temporal lobe complex partial seizures may produce bizarre behaviors that do not correspond to classic ES findings and may not produce discernible abnormalities with scalp-electrode EEG (and therefore may be misdiagnosed even with video-EEG monitoring, although this is more likely with partial seizures than with generalized). A multidisciplinary team approach may be required.

History: Attempt to document: prodromal symptoms, precipitating factors, time and environment of Sz, mode and duration of progression, ictal and postictal events, frequency and stereotypy of manifestations. Determine if patient has history of psychiatric conditions, and if they are acquainted with individuals who have ES.

Psychological testing: May help. Differences occur in ES and NES on the Minnesota Multiphasic Personality Inventory **(MMPI)** scales in hypochondriasis, depression hysteria, and schizophrenia[34].

Table 17-4 contrasts some features of true seizures vs. NES, and *Table 17-5* lists some features often associated with NES, however, no characteristics are definitively diagnostic of NES since a number of them may also occur with ES.

Features common to both true seizures and NES: verbal unresponsiveness, rarity of automatisms and whole-body flaccidity, rarity of urinary incontinence. Reminder: some seizures can be bizarre and can resemble NES (sometimes called pseudo-pseudoseizures). 10% of patients with psychogenic seizures actually have epilepsy.

Table 17-4 Features of ES vs. NES[31]

Feature	Epileptic seizure	NES
% males	72%	20%

Clonic UE movement		
inphase	96%	20%
out-of-phase	0	56%
Clonic LE movement		
inphase	88%	16%
out-of-phase	0	56%
Vocalizations		
none	16%	56%
start of seizure	24%	44%
middle	60% "epileptic cry"	0
types	only sounds of tonic or clonic respiratory muscle contraction	moans, screams, grunts, snorts, gagging, retching, understandable statements, gasps
Head turning		
unilateral	64%	16%
side-to-side	8% (slow, low amplitude)	36% (violent, high amplitude)

Features suggestive of non-epileptic seizures:

1. arching of the back: 90% specific for NES
2. asynchronous movement
3. stop & go: seizures usually build and then gradually subside
4. forced eye closing during entire seizure
5. provoked with stimuli that would not cause a seizure (e.g. tuning fork to the head, alcohol pad to the neck, IV saline…)
6. bilateral shaking with preserved awareness. Exception: supplementary motor area seizures (mesial frontal area) these seizures are usually tonic (not clonic)
7. weeping (whining): highly specific
8. multiple or variable seizure types (ES is usually stereotypical), fluctuating level of consciousness, denial of correlation of Sz with stress

If any two of the following are demonstrated, 96% of time this will be NES:

1. out-of-phase clonic UE movement
2. out-of-phase clonic LE movement
3. no vocalization or vocalization at start of event

Lateral tongue laceration is very specific for seizures.

Table 17-5 Features often associated with NES[30]

• frequent seizures despite therapeutic AEDs
• multiple different-physician visits
• lingering prodrome or gradual ictal onset (over minutes)
• prolonged duration (> 5 mins)
• manifestations altered by distraction
• suggestible or inducible seizures
• intermittent arrhythmic and out-of-phase activity
• fluctuating intensity and severity during Sz
• side-to-side rolling, pelvic thrusting, wild movements
• bilateral motor activity with preserved consciousness
• nonphysiologic spread of neurologic signs
• absence of labored breathing or drooling after generalized convulsion
• expression of relief or indifference
• crying or whimpering
• no postictal confusion or lethargy
• disproportionate postictal mental status changes
• absence of stereotypy

Prolactin levels after seizures

Transient elevations in human serum prolactin **(HSP)** levels occur following 80% of generalized motor, 45% of complex partial, and only 15% of simple partial seizures[35]. Peak levels are reached in 15-20 minutes, and gradually return to baseline over the subsequent hour[36-38]. It has been suggested that drawing a serum prolactin level shortly after a questionable seizure may be helpful in differentiating NES (which may have elevated cortisol levels but normal HSP levels[39]).

Repetitive seizures are associated with progressively smaller HSP elevations[40], and no rise follows absence seizures or status epilepticus (whether convulsive or absence)[41]. Greater than twofold HSP elevations consistently follow seizures that produce intense widespread high frequency mesial temporal lobe discharges; whereas such elevations do not occur in seizures not involving these limbic structures[42].

Furthermore, there may be higher baseline HSP levels in cases with right-sided interictal EEG discharges compared to those with left-sided[43], and the presence of psycho-pathology may affect postictal HSP elevations[44].

Therefore, the presence of HSP peaks may be strongly indicative of true

seizures, but the absence may be due to a variety of complex phenomena[45]. The overall classification accuracy is ≈ 72%[38].

17.2.5. Febrile seizures

Definitions[46]

febrile seizure	a seizure in infants or children associated with fever with no defined cause and unaccompanied by acute neurologic illness (includes seizures during vaccination fevers)
complex febrile seizure	a convulsion that lasts longer than 15 minutes, is focal, or multiple (more than one convulsion per episode of fever)
simple febrile seizure	not complex
recurrent febrile seizure	more than one episode of fever associated with seizures

Epidemiology[46]

Febrile convulsions are the most common type of seizure. Excluding children with pre-existing neurologic or developmental abnormalities, the prevalence of febrile seizures is ≈ 2.7% (range: 2-5% in U.S. children aged 6 mos-6 yrs). The risk for developing epilepsy after a simple febrile seizure is ≈ 1%, and for a complex febrile seizure is 6% (9% for prolonged seizure, 29% for focal seizure). An underlying neurological or developmental abnormality or a family history of epilepsy increases the risk of developing epilepsy.

Treatment

In one study, the IQ in the group treated with phenobarbital was 8.4 points lower (95% confidence interval) than the placebo group, and there remained a significant difference several months after discontinuing the drug[47]. Furthermore, there was no significant reduction in seizures in the phenobarbital group. And yet, no other drug really appears well suited to treating this entity: carbamazepine and phenytoin appear ineffective, valproate may be effective but has serious risks in the < 2 yrs age group. Given the low incidence (1%) of

having *afebrile* seizures (i.e. epilepsy) after a simple febrile seizure and the fact that AEDs probably do not prevent this development, there is little support for prescribing anticonvulsants in these cases. The recurrence rate of febrile seizures in children with a history of one or more febrile seizure can be reduced by administering diazepam 0.33 mg/kg PO q 8 hrs during a febrile episode (temp > 38.1° C) and continuing until 24 hrs after the fever subsides[48].

17.3. Status epilepticus

Key concepts:

- definition: Sz > 5 mins, or persistent Sz after 1st & 2nd line AEDs
- morbidity and mortality are high in untreated status epilepticus **(SE)**
- most common etiology: patient with known Sz disorder with low AED levels
- de novo SE in acute illness is considered a manifestation of the illness which should be treated at the same time as the SE
- see *Table 17-6*, page 405 for treatment measures

Definition: a seizure lasting > 5 minutes or persistent seizure activity after sequential administration of appropriate first and second-line AEDs[49].

Features important to management

- seizures that do not cease in 5-10 mins are less likely to terminate[50]
- in patients with no prior Sz history, status epilepticus **(SE)** is usually a manifestation of illness-related cortical irritation or injury[49] and treatment of the underlying disorder (in addition to treating the SE) is critical
- a relapse of Sz. in a patient with a known Sz. disorder and subtherapeutic AED levels usually responds to a bolus of the maintenance AEDs. However, SE should be treated by the standard protocol[49]
- most cases of convulsive status in adults start as partial seizures that generalize
- the choice of 1st and 2nd-line AEDs is arbitrary, and the dose is the more important determinant of success in aborting SE[49]

Types of status epilepticus

• generalized status

1. convulsive: generalized convulsive tonic-clonic status epilepticus **(SE)** is the most frequent type[51]. A medical emergency
2. absence[A]
3. secondarily generalized: accounts for ≈ 75% of generalized SE
4. myoclonic
5. atonic (drop attack): especially in Lennox-Gastaut syndrome (*see page 396*)

• partial status (usually related to an anatomic abnormality)

1. simple (AKA **epilepsy partialis continuans**)
2. complex[A]: most often from frontal lobe focus. Urgent treatment is required
3. secondarily generalized

A. in status, these may present in **twilight state**

Epidemiology

Incidence is ≈ 150,000 new cases/year in the U.S. in the outpatient setting[49]. Most cases occur in young children (among children, 73% were < 5 yrs old[52]), the next most affected group is patients > 60 yrs age. In > 50% of cases, SE is the patient's first seizure[51]. One out of six patients presenting with a first time seizure will present in SE

Etiologies

1. the most common etiology is a patient with a known seizure disorder having low AED levels for any reason (non-compliance, intercurrent infection preventing PO intake of meds, drug-drug interactions → lowering effectiveness of AEDs…)
2. febrile seizures: a common precipitator in young patients. 5-6% of patients presenting with SE have a history of prior febrile seizures
3. cerebrovascular accidents: the most commonly identified cause in the elderly
4. CNS infection: in children, most are bacterial, the most common organisms were *H. influenza* and *S. pneumoniae*

5. idiopathic: accounts for ≈ one-third (in children, usually associated with fever)
6. epilepsy: is present or is subsequently diagnosed in ≈ 50% of patients presenting with SE. About 10% of adults ultimately diagnosed as having epilepsy will present in SE
7. **electrolyte imbalance**: hyponatremia (most common in children, usually due to water intoxication[52]), hypoglycemia, hypocalcemia, uremia, hypomagnesemia…
8. illicit drug intoxication: especially cocaine, amphetamines
9. precipitous drug withdrawal: barbiturates, benzodiazepines, alcohol or narcotics
10. proconvulsant drugs, including: ß-lactam antibiotics (penicillins, cephalosporins), certain antidepressants (bupropion), clonazapine, bronchodilators, immunosuppressants
11. traumatic brain injury: acute as well as old
12. hypoxia/ischemia
13. tumor

In children < 1 yr age, 75% had an acute cause: 28% were secondary to CNS infection, 30% due to electrolyte disorders, 19% associated with fever[52]. In adults, a structural lesion is more likely. In an adult, the most common cause of SE is subtherapeutic AED levels in a patient with a known seizure disorder.

Morbidity and mortality from SE

Mean duration of SE in patients without neurologic sequelae is 1.5 hrs (therefore, proceed to pentobarbital anesthesia before ≈ 1 hour of SE). Recent mortality: < 10-12% (only ≈ 2% of deaths are directly attributable to SE or its complications; the rest are due to the underlying process producing the SE). Mortality in lowest amongst children (≈ 6%[52]), patients with SE related to subtherapeutic AEDs, and patients with unprovoked SE[53]. The highest mortality occurs in elderly patients and those with SE resulting from anoxia or CVA[53]. 1% of patients die during the episode itself.

Morbidity and mortality is due to[54]:

1. CNS injury from repetitive electric discharges: irreversible changes begin to appear in neurons after as little as 20 minutes of convulsive activity. Cell death is very common after 60 mins
2. systemic stress from the seizure (cardiac, respiratory, renal, metabolic)

3. CNS damage by the acute insult that provoked the SE

17.3.1. General treatment measures for status epilepticus

Treatment is directed at stabilizing the patient, stopping the seizure, and identifying the cause (determining if there is an acute insult to the brain) and if possible also treating the underlying process. Treatment often must be initiated prior to the availability of test results to confirm the diagnosis.

- CPR if needed
- neurologic exam
- "ABC's"
  - **A** irway: oral airway if feasible. Turn patient on their side to avoid aspiration
  - **B** reathing: O_2 by nasal cannula or bag-valve-mask. Consider intubation if respirations compromised or if seizure persists > 30 min
  - **C** irculation: large bore proximal IV access (2 if possible): start with NS KVO
- monitor: EKG & baseline vital signs. Pulse oximeter. Frequent blood pressure checks
- bloodwork: STAT capillary blood (fingerstick) glucose (to R/O hypoglycemia), electrolytes (including glucose), CBC, LFTs, Mg^{++}, Ca^{++}, AED levels, ABG
- head CT (usually without contrast)
- correct any electrolyte imbalance (SE due to electrolyte imbalance responds more readily to correction than to AEDs[52])
- if CNS infection is a major consideration, perform LP for CSF analysis (especially in febrile children) unless contraindicated (*see page 201*). WBC pleocytosis up to 80 x 106/L can occur following SE (benign postictal pleocytosis), and these patients should be treated with antibiotics until infection can be ruled out by negative cultures
- <u>general</u> meds for unknown patient:
  1. glucose:
     A. in patients with poor nutrition (e.g. alcoholics): giving glucose in thiamine deficiency can precipitate Wernicke's encephalopathy (*see page 275*) ∴ prior to glucose bolus give thiamine 50-100 mg IV
     B. if fingerstick glucose can be obtained immediately and it shows hypoglycemia, or if no fingerstick glucose can be done: give 25-50 ml

of D50 IV push for adults (2 ml/kg of 25% glucose for peds). If at all possible, draw blood for definitive serum glucose first

2. naloxone (Narcan®) 0.4 mg IVP (in case of narcotics)
3. ± bicarbonate to counter acidosis (1-2 amps depending on length of seizure)
4. for neonate < 2 years: consider pyridoxine 100 mg IV push (pyridoxine-dependent seizures constitute a rare autosomal recessive condition that generally presents in the early neonatal period[50])

- administer specific anticonvulsants for seizures lasting > 5-10 mins (*see below*)
- EEG monitor if possible
- if paralytics are used (e.g. to intubate), use short acting agents and be aware that muscle paralysis alone may stop visible seizure manifestations, but does not stop the electrical seizure activity in the brain, which can lead to permanent neurologic damage if prolonged (*see above*)

17.3.2. Medications for generalized convulsive status epilepticus

There are no randomized trials for refractory status epilepticus, although there is published data regarding specific treatment options. Numerous protocols exist. *Table 17-6* shows a summary of medications for a status epilepticus protocol that is outlined in further detail below (modified management scheme[49]). Items below in boxes are considered treatment of choice. "Adult" refers to patients > 16 yrs of age. Drugs should be given IV (do not use IM route). If IV access is impossible, diazepam solution (not suppository) or Diastat® (diazepam rectal) can be given rectally or intranasal, buccal[55] or rectal midazolam (Versed®) can be given.

Rapid treatment is indicated as delays are associated with neuronal injury and reduced response to medications.

Table 17-6 Summary of initial steps for status epilepticus (adult) (*see text* for details)

ABC's. Start O_2. Turn patient on their side. Check VS. Do a neuro exam
Monitor/labs: Pulse oximetry. EKG/telemetry. ✔ Fingerstick glucose. Blood tests (do not wait for results to begin Rx): ✔ electrolytes, ✔ CBC, ✔ ABG, ✔ AED levels, ✔ LFTs, ✔ Mg^{++}, ✔ Ca^{++}, ✔ head CT
Large bore IV X 2. Start IV fluids

• **thiamine** 100 mg IV and/or 50 ml of 50% dextrose (if needed)
First-line AED: • **lorazepam** (Ativan®) 0.1 mg/kg IV @ < 2 mg/min
Second-line AED: (may be given simultaneously with first-line drug or 1 minute after end of lorazepam bolus if Sz persist) • **phenytoin***/fosphenytoin 20 mg/kg IV loading dose starting at 25 mg/min for phenytoin, or 75 mg/min for fosphenytoin • then, titrate phenytoin/fosphenytoin infusion up to max* as tolerated
✔ phenytoin level ≈ 10 min after PHT loading dose
± 3rd line AED. NB: only 7% chance of stopping Sz with 3rd line drugs. (Consider: skipping 3rd line and intubate & start CIT below). Select one: • phenobarbital: up to 20 mg/kg IV (start infusing @ < 100 mg/min • sodium valproate 15-30 mg/kg IV bolus (max rate: 6 mg/kg/min) • levetiracetam 20mg/kg IV bolus of over 15 minutes
CIT: If seizures continue > 30 mins or if skipping 3rd line drugs: intubate in ICU and begin continuous infusion therapy **(CIT)** of midazolam, pento-barbital or propofol (*see text*). If Sz persist, ensure that correctable conditions have been ruled-out and/or treated; continue to following steps
alternative CIT: carbamazepine, oxcarbazepine, topiramate, lamotrigine…
novel therapeutic options (not systematically studies): shock therapy…

* maximum rate for phenytoin IV is 50 mg/min; for fosphenytoin it is 150 mg PE/min (*see page 411*) if BP stable

Protocol for status epilepticus (SE) in <u>adult</u>[49]

Prehospital phase:

1. impending SE: may be heralded by a crescendo in Sz. A 1-3 d course of lorazepam may preempt the development of SE
2. SE treatment may be initiated with buccal midazolam or rectal diazepam

Hospital phase:

Start IV drugs at half the maximal rate, and titrate up to maximal rate if VS stable.

1. First line drugs
   A. benzodiazepine[56] (main side effect: respiratory depression in ≈ 12%; be prepared to intubate). Onset of action is rapid (1-2 mins):

• **lorazepam** (Ativan®) **0.1 mg/kg** (about 4 mg for average adult) IV @ rate < 2 mg/min (range: 0.02-0.12 mg/kg)

OR diazepam (Valium®) 0.1 mg/kg (7 mg average adult dose) IV @ rate < 50 mg/min. IV diazepam redistributes rapidly and SE may recur within a few minutes. Rectal dose (usually absorbed in ≈ 10 mins): 0.5 mg/kg of diazepam solution up to 20 mg max, or

Diastat® 0.2 mg/kg

OR midazolam (Versed®) 0.05 mg/kg IV @ < 0.01 mg/min, or 10 mg buccal

- Wait 1 minute for response. If Sz continue, given additional doses of lorazepam up to a maximum of 9 mg (adult)

2. Second line drugs: either start simultaneously with 1st line drugs, or give if Sz persist 1 minute after first-line benzodiazepine dose
   A. in second IV site: load with phenytoin (Dilantin®) **(PHT)**[57] as follows (do not worry about acutely overdosing, but do follow dosing rates, monitor BP for hypotension and EKG for arrhythmias). Conventional phenytoin can only be given in NS to prevent precipitation. After giving the following loading dose, start on maintenance (*see page 409*)

      1. **phenytoin** load with **20 mg/kg** (if not already on PHT): (1400 mg for 70 kg adult) (use 15 mg/kg for elderly patients), maximum rate for phenytoin **< 50 mg/min** (fosphenytoin max rate is 150 mg PE/min)
      2. if on PHT and a recent level is known: a rule of thumb is giving 0.74 mg/kg to an adult raises the level by ≈ 1 μg/ml
      3. if on PHT and level not known: adult: give 500 mg @ < 50 mg/min[A]

3. Third line drugs: only 7% of patients who have not responded to the above will respond to a 3rd line drug[56]. Therefore, third line drugs may be skipped and one may proceed directly to CIT (*see below*)
   A. PHT additional doses of 5 mg/kg @ < 50 mg/min up to a total of 30 mg/kg
   B. one of the following[B]

      - phenobarbital: up to 20 mg/kg IV (1400 mg for 70 kg) (start infusing @ < 100 mg/min until seizures stop), takes 15-20 min to work, watch BP (a myocardial depressant).
        Peds: 5-10 mg/kg/dose q 20-30 min to max total 30-40 mg/kg.

        Phenobarbital may be preferred to PHT in patients with PHT hypersensitivity, cardiac conduction abnormality, and in neonates and young children. Maintenance phenobarbital therapy should be instituted with 24 hours of the loading dose (*see page 413*), OR
      - sodium valproate 15-30 mg/kg IV bolus (max rate of 6 mg/kg/min), followed by maintenance dose of 500 mg TID, OR

• levetiracetam 20mg/kg IV bolus of over 15 minutes, followed by maintenance dose of 1500 mg BID

C. initiate EEG monitoring in the ICU

4. Continuous infusion therapy **(CIT)**: if seizures continue > 30 minutes, intubate and begin any one of the following:

• midazolam: load with 0.2 mg/kg slow IV bolus, maintenance 0.1-0.4 mg/kg/hr, titrate up to a maximum of 2.0 mg/kg/hr

• propofol: loading dose: 1-2 mg/kg IV at 10 mg/min, maintenance 2-10 mg/kg/h, maximum dose: 15 mg/kg/h (varies according to institution)

• pentobarbital: load with 3 mg/kg IV at a rate of 25 mg/min, maintenance 0.3-3 mg/kg/hr. Monitor BP, for hypotension give fluids and dopamine (*see page 884* for additional measures such as PA catheter)

5. if seizures continue: additional drugs that may be tried include carbamazepine, oxcarbazepine, topiramate, levetiracetam, lamotrigine, gabapentin…

6. novel treatments: lidocaine infusion, inhalational anesthesia, direct brain stimulation, transcranial magnetic stimulation, electroconvulsive therapy (shock therapy), surgical intervention if a seizure focus is identified

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A. the risk of acute phenytoin toxicity in the hospital setting is lower than that of continued SE, the therapeutic levels used for drugs is based on chronic treatment in the outpatient setting[49]

B. using both phenobarbital and a benzodiazepine (e.g. diazepam) is discouraged because of increased risk of respiratory depression

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Efficacy

Diazepam stops seizures within 3 mins in 33%, within 5 mins in 80%. PHT stops seizures in 30% after 400 mg has been given. 63% of generalized tonic-clonic SE respond to benzodiazepine + PHT. PHT is slower to control status than diazepam, but lasts longer.

Lorazepam

Among benzodiazepines, lorazepam **(LZP)** is preferred (diazepam **(DZP)** redistributes rapidly in fatty tissues[58], and seizures may recur within 10-20 minutes), but causes longer sedation. LZP aborts SE in 97% of cases, vs. 68% for DZP[59]. Also, less respiratory depression than with DZP. As with all

benzodiazepines:

1. respiratory depression and hypotension are exacerbated when used with other depressants (including barbiturates…)
2. effectiveness in SE is reduced by prior maintenance on other benzodiazepines (e.g. clonazepam), but is not affected by the presence of other anticonvulsants
3. tachyphylaxis may develop so that subsequent doses are less effective[60]

Medications to avoid in status epilepticus

1. narcotics
2. phenothiazines: including promethazine (Phenergan®)
3. neuromuscular blocking agents without AED therapy: seizures may continue and cause neurologic injury but would not be clinically evident (*see page 404*)

17.3.3. Miscellaneous status epilepticus

Myoclonic status

Treatment: valproic acid (drug of choice). Place NG, give 20 mg/kg per NG loading dose. Maintenance: 40 mg/kg/d divided (*see page 412*).

Can add lorazepam (Ativan®) or clonazepam (Klonopin®) to help with acute control.

Absence status epilepticus

Almost always responds to diazepam.

17.4. Antiepileptic drugs (AEDs)

The goal of AEDs is seizure control (a contentious term, usually taken as reduction of seizure frequency and severity to the point to permit the patient to live a normal lifestyle without epilepsy-related limitations) with minimal or no drug toxicity. ≈ 75% of epileptics can achieve satisfactory seizure control with medical therapy[61].

17.4.1. Classification of AEDs

AEDs can be grouped as shown in *Table 17-7*.

The following agents are considered "broad spectrum" (treat a variety of seizure types):

1. valproic acid
2. lamotrigine (Lamictal®)
3. levetiracetam (Keppra®)

These agents are not considered broad spectrum:

1. phenytoin (Dilantin® and others)
2. carbamazepine (Tegretol®)

Agents that interfere with platelet function and may ↑ the risk of bleeding complications:

1. valproic acid
2. phenytoin (Dilantin® and others)

17.4.2. Choice of antiepileptic drug

Antiepileptic drugs (AED) for various seizure types

Boldface drugs are drug of choice **(DOC)**.

1. primary generalized
   A. GTC (generalized tonic-clonic):
      1. **valproic acid** (VA): if no evidence of focality some studies show fewer side effects and better control than PHT (*see page 412*)
      2. carbamazepine: *see page 411*
      3. **phenytoin** (PHT): *see page 409*
      4. phenobarbital (PB): *see page 413*
      5. primidone (PRM): *see page 413*

   B. absence:
      1. **ethosuximide**
      2. **valproic acid** (VA)
      3. clonazepam
      4. methsuximide: *see page 414*

   C. myoclonic → benzodiazepines

D. tonic or atonic:
1. benzodiazepines
2. felbamate: *see page 414*
3. vigabatrin: *see page 417*

2. partial (simple or complex, with or without secondary generalization)[62] (VA may compare favorably with CBZ for secondarily GTC, but is less effective for complex partial seizures[63]):

A. **carbamazepine** (CBZ)	most effective, least side effects
C. phenobarbital (PB)	↓
B. **phenytoin** (PHT)	↓
D. primidone (PRM)	slightly less effective, more side effects

3. second line drugs for any of the above seizure types:
A. valproate
B. lamotrigine[A]: *see page 417*
C. topiramate[A]: *see page 417*

A. effective for many types of generalized seizures, but are not FDA approved for this yet

Table 17-7 Classification of AEDs

Drug	Indications*	Page
• Barbiturates		
pentobarbital (Nembutal®)	**status**	
phenobarbital	**status**, **GTC**, **partial Sz**, febrile Sz, neonatal Sz	413
primidone (Mysoline)®		413
• Benzodiazepines		
clonazepam (Klonopin®)	**Lennox-Gastaut**, **akinetic**, **myoclonic**	415
clorazepate (Tranxene-SD®)	**adj - partial Sz**	
diazepam (Valium®)	**status**	405
lorazepam (Ativan®)	**status**	405
• GABA analogues		
gabapentin (Neurontin®)	**adj - partial Sz**	416
tiagabine (Gabitril®)	**adj - partial Sz**	418
• Hydantoins		

fosphenytoin (Cerebyx®)	**status**, **Sz during neurosurgery**, **short-term replacement for oral PHT**	411
phenytoin (Dilantin®)	**GTC**, **CP**, **Sz during or after neurosurgery**	409
• Phenyltriazenes		
lamotrigine (Lamictal®)	**adj - partial Sz**, **adj - Lennox-Gastaut**	417
• Succinimides		
ethosuximide (Zarontin®)	**ABS**	414
methsuximide (Celontin®)	**ABS** refractory to other drugs	414
• Miscellaneous		
acetazolamide (Diamox®)		416
carbamazepine (Tegretol®, Carbatrol®)	**partial Sz + complex symptomology**, **GTC**, **mixed Sz**, ✖ not for absence	411
felbamate (Felbatol®)	use only with extreme caution - *see text*	414
levetiracetam (Keppra®)	**adj - partial Sz**	415
oxcarbazepine (Trileptal®)	**mono or adj - partial Sz**	412
topiramate (Topamax®)	**adj - partial Sz** or **primarily GTC**	417
valproate (Depakene®…)	**CP (alone or with other types)**, **ABS**, **adj - multiple Sz types**	412
zonisamide (Zonegran®)	**adj - partial Sz**	

* Indications for seizure types (does not include other uses, e.g. for chronic pain). FDA approved indications are in bold, off-label indications appear in plain text.
Abbreviations: ABS = absence, adj = adjunctive therapy, CP = complex partial, GTC = generalized tonic-clonic, PHT = phenytoin, Sz = seizure, status = status epilepticus

17.4.3. Anticonvulsant pharmacology[64]

GENERAL GUIDELINES

Monotherapy versus polytherapy

1. increase a given medication until seizures are controlled or side effects become intolerable (do not rely solely on therapeutic levels, which is only the range in which most patients have seizure control without side effects)
2. try monotherapy with a different drugs before resorting to two drugs together. 80% of epileptics can be controlled on monotherapy, however, failure of monotherapy indicates an 80% chance that the seizures will not be controllable pharmaco-logically. Only ≈ 10% benefit significantly from

the addition of a second drug[63]. When > 2 AEDs are required, consider nonepileptic seizures (*see page 400*)

3. when first evaluating patients on multiple drugs, withdraw the most sedating ones first (usually barbiturates and clonazepam)

Generally, dosing intervals should be less than one half-life. Without loading dose, it takes about 5 half-lives to reach steady state.

Many AEDs affect liver function tests **(LFTs)**, however, only rarely do the drugs cause enough hepatic dysfunction to warrant discontinuation. Guideline: discontinue an AED if the GGT exceeds twice normal.

SPECIFIC ANTICONVULSANTS

Table 17-8 Abbreviations

AED = antiepileptic drug; **ABS** = absence; **EC** = enteric coated; **DIV** = divided; **DOC** = drug of choice; **GTC** = generalized tonic-clonic seizure; **S/C-P** = simple or complex partial.
Pharmacokinetics: Unless otherwise specified, numbers are given for oral dosing form. $\mathbf{t_{1/2}}$ = half-life; $\mathbf{t_{PEAK}}$ = time to peak serum level; $\mathbf{t_{SS}}$ = time to steady state (approximately 5 **x** $t_{1/2}$); $\mathbf{t_{D/C}}$ = time to discontinue (recommended withdrawal period over which drug should be tapered); **MDF** = minimum dosing frequency. "Therapeutic level" is the average therapeutic range.

phenytoin (PHT) (Dilantin®) DRUG INFO

INDICATIONS

GTC, S/C-P, occasionally in ABS.

PHARMACOKINETICS

Pharmacokinetics are complicated: at low concentrations, kinetics are 1st order (elimination proportional to concentration), metabolism saturates near the therapeutic level resulting in zero-order kinetics (elimination at a constant rate). ≈ 90% of total drug is protein bound. Oral bioavailability is ≈ 90% whereas IV bioavailability is ≈ 95%; this small difference may be significant when patients are near limits of therapeutic range (due to zero-order kinetics).

$t_{1/2}$ (half-life)	t_{PEAK} (peak serum levels)	t_{SS} (steady state)	$t_{D/C}$ (discontinue)	Therapeutic level*
≈ 24 hrs (range: 9-140 hrs)†	oral suspension: 1.5-3 hrs regular capsules: 1.5-3 hrs extended release capsules: 4-12 hrs	7-21 days	4 wks	10-20 µg/ml

* therapeutic level as measured in most labs: 10-20 µg/ml (NB: it is the free PHT that is the important moiety; this is usually ≈ 1% of total PHT, thus therapeutic free PHT levels are 1-2 µg/ml; some labs are able to measure free PHT directly).

† $t_{1/2}$ for phenytoin depends on serum concentration and metabolic autoinduction

Renal failure: dosage adjustment not needed. However, serum protein binding may be altered in uremia which can obfuscate interpretation of serum phenytoin levels. *Eq 17-1* may be used to convert serum PHT concentration in a uremic patient C (observed), to the expected PHT level in nonuremic patients C (nonuremic).

$$C\ (\text{nonuremic}) = \frac{C\ (\text{observed})}{0.1 \times \text{albumin} + 0.1} \qquad \textbf{Eq 17-1}$$

ORAL DOSE

***Rx* Adult**: usual maintenance dose= 300-600 mg/d divided BID or TID (MDF = q d, for single daily dosing, either the phenytoin-sodium capsules or the extended release form should be used). Oral loading dose: 300 mg PO q 4 hrs until 17 mg/kg are given. **Peds**: oral maintenance: 4-7 mg/kg/d (MDF = BID). **SUPPLIED**: (oral forms): 100 mg tablets of phenytoin-sodium (sodium-salt); 30 & 100 mg Kapseals® (extended release); 50 mg chewable Infatabs® (phenytoin-acid); oral suspension 125 mg/5-ml in 8 oz. (240 ml) bottles or individual 5 ml unit dose packs; pediatric suspension 30 mg/5-ml. Phenytek® 200 & 300 mg capsules.

Dosage changes

Because of zero-order kinetics, at near-therapeutic levels a small dosage change can cause large level changes. Although computer models are necessary for a high degree of accuracy, the dosing change guidelines in *Table 17-9* or the nomogram in *Figure 17-1*[65] may be used as a quick approximation.

GI absorption of phenytoin suspension or capsules may be decreased by up to 70% when given with nasogastric feedings of Osmolyte® or Isocal®[66, 67], and the sus-pension has been reported to have erratic absorption. Hold NG feeding for 2 hrs before and 1 hour after phenytoin dose.

Table 17-9 Guidelines for changing phenytoin dosage

Present level (mg/dl)	Change to make
< 6	100 mg/day
6-8	50 mg/day
> 8	25-30 mg/day

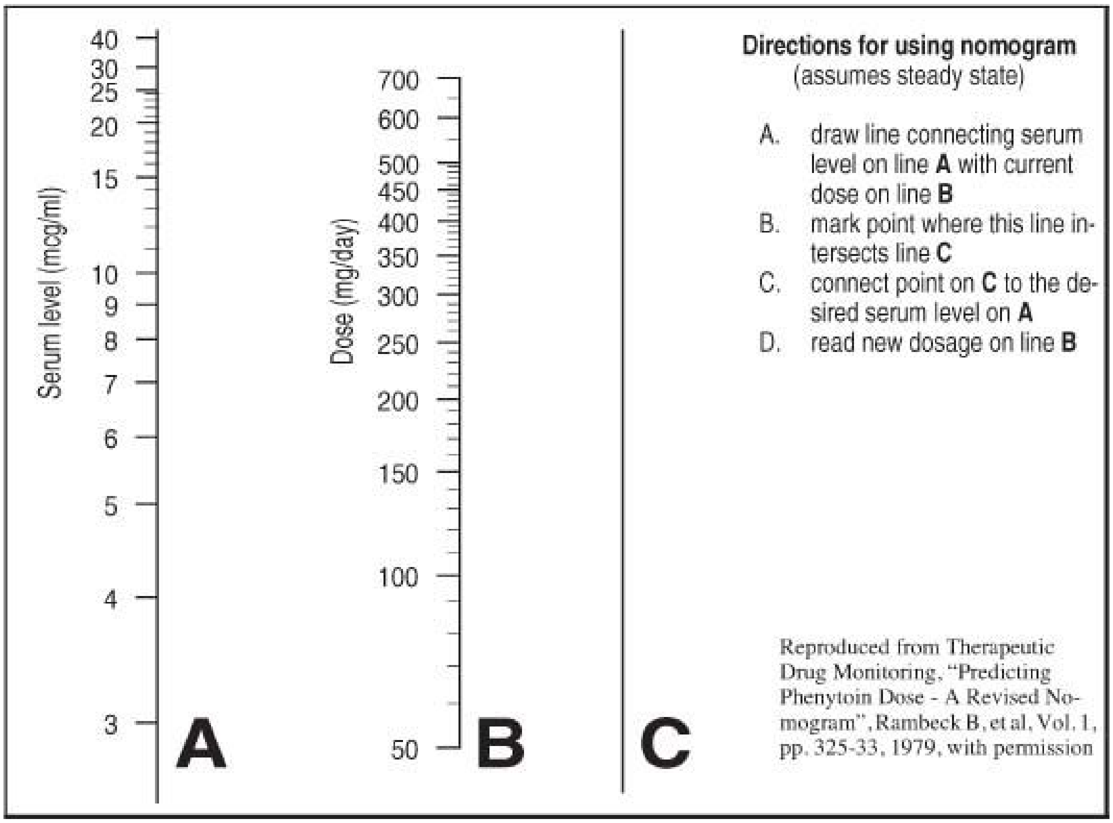

Figure 17-1 Nomogram for adjusting phenytoin dose

PARENTERAL DOSE

Phenytoin is a negative inotrope and can cause hypotension.

Conventional phenytoin may be given slow IVP or by IV drip (*see below*). The IM route should NOT be used (unreliable absorption, crystallization and sterile abscesses may develop). IV must be given slowly to reduce risk of arrhythmias and hypotension, viz. **Adult**: < 50 mg/min, **Peds**: < 1-3 mg/kg/min. The only compatible solution is NS, inject at site nearest vein to avoid precipitation.

Rx loading. Adult: 18 mg/kg slow IV. Peds: 20 mg/kg slow IV.

Rx maintenance. Adult: 200-500 mg/d (MDF = q d). Most adults have therapeutic levels on 100 mg PO TID. Peds: 4-7 mg/kg/d (MDF = BID).

Drip loading method:

Requires cardiac monitoring, and BP check q 5 minutes.

Rx Add 500 mg PHT to 50 ml NS to yield 10 mg/ml, run at 2 ml/min (20 mg/min) long enough to give 18 mg/kg (for 70 kg patient: 1200 mg over 60 mins). For more rapid administration, up to 40 mg/min may be used, or use fosphenytoin (*see below*). Decrease rate if hypotension occurs.

Fosphenytoin sodium injection

Fosphenytoin sodium **(FOS)** injection (Cerebyx®) is a newer formulation for administering IV phenytoin, and is indicated for short term use (≤ 5 days) when the enteral route is not usable. It is completely converted in vivo to phenytoin by organ and blood phosphatases with a conversion half-life of 10 minutes. Product labeling is given in terms of phenytoin equivalents **(PE)**. Safety in pediatric patients has not been established. **SUPPLIED**: 50 mg PE/ml in 2 & 10 ml vials (100 mg PE and 500 mg PE respectively).

Advantages of FOS (over conventional IV phenytoin):

1. less venous irritation (due to lower pH of 8.6-9 compared to 12 for phenytoin) resulting in less pain and IV extravasation
2. FOS is water soluble and therefore may be infused with dextrose or saline
3. tolerated by IM injection (IM route should not be used for status epilepticus)
4. does not come combined with propylene glycol (which can cause cardiac arrhythmias and/or hypotension itself)
5. the maximum administration rate is 3 **x** as fast (i.e. 150 mg PE/min)

SIDE EFFECTS OF PHENYTOIN

May interfere with cognitive function. May produce SLE-like syndrome, hepatic granulomas, megaloblastic anemia, cerebellar degeneration (chronic doses), hirsutism, gingival hypertrophy, hemorrhage in newborn if mother on PHT, toxic epidermal necrolysis (Stevens-Johnson variant). PHT antagonizes vitamin D → osteomalacia and rickets. Most hypersensitivity reactions occur within 2 months of initiating therapy[66]. In cases of maculopapular erythematous rash, the drug may be stopped and the patient may be re-challenged; often the rash will not recur the second time. Teratogenic (fetal hydantoin syndrome[68]).

Signs of phenytoin toxicity may develop at concentrations above 20 µg/ml (toxicity is more common at levels > 30 µg/ml) and include nystagmus (may also occur at therapeutic levels), diplopia, ataxia, asterixis, slurred speech, confusion, and CNS depression.

Drug-drug interactions: fluoxetine (Prozac®) results in elevated phenytoin levels (ave: 161% above baseline)[69]. Phenytoin may impair the efficacy of: corticosteroids, warfarin, digoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

carbamazepine (CBZ) (Tegretol®) DRUG INFO

INDICATIONS

Partial seizures with or without secondary generalization. Trigeminal neuralgia. An IV form for use in e.g. status epilepticus is in development.

DOSE

***Rx* oral route. Adult** range: 600-2000 mg/d. **Peds**: 20-30 mg/kg/d. MDF = BID.

Before starting, check: CBC & platelet count (consider reticulocyte count) & serum Fe. Package insert says "recheck at frequent intervals, perhaps q week **x** 3 mos, then q month **x** 3 yrs."

Do not start CBZ (or discontinue it if patient already on CBZ) if: WBC < 4K, RBC < 3 **x** 10^6, Hct < 32%, platelets < 100K, reticulocytes < 0.3%, Fe > 150 µg%.

Start low and increment slowly: 200 mg PO q d **x** 1 wk, BID **x** 1 wk, TID **x** 1 wk. As an inpatient, dosage changes may be made every 3 days, monitoring for signs of side effects. As an outpatient, changes should be made only ≈ weekly, with levels after each change. **Carbatrol**® (extended release CBZ) is usually dosed BID.

SUPPLIED: oral form. Scored tabs 200 mg. Chewable scored tabs 100 mg. Suspension 100 mg/5-ml. IV form: not available in the U.S. at the time of this writing. Carbatrol® (extended release CBZ): 200 & 300 mg tablets.

Caveats with oral forms: oral absorption is erratic, and smaller more frequent doses are preferred[70]. Oral suspension is absorbed more readily, and also ✖ should not be administered simultaneously with other liquid medicinal agents as it may result in the precipitation of a rubbery, orange mass. ✖ May aggravate hyponatremia by SIADH-like effect.

PHARMACOKINETICS

$t_{1/2}$ (half-life)	t_{PEAK} (peak levels)	t_{SS} (steady state)	$t_{D/C}$ (discontinue)	Therapeutic level (µg/ml)*
single dose: 20-55 hrs after chronic therapy: 10-30 hrs (adults), 8-20 hrs (peds)	4-24 hrs	up to 10 days†	4 wks	6-12

* may be misleading since the active metabolite carbamazepine-10,11-epoxide may cause toxicity and must be assayed separately

† t_{SS} may subsequently fall due to autoinduction which plateaus at 4-6 wks

CBZ induces hepatic enzymes that result in increased metabolism of itself (autoinduction) as well as other drugs over a period of ≈ 3-4 weeks.

SIDE EFFECTS

✖ Drug-drug interaction: caution, propoxyphene (Darvon®), cimetidine, erythromycin and isoniazid may cause dramatic elevation of CBZ levels due to inhibition of hepatic cytochrome oxidase that degrades CBZ[71]. Side effects include:

1. drowsiness and GI upset: minimized by slow dose escalation
2. relative leukopenia in many: usually does not require discontinuing drug
3. transient diplopia
4. ataxia
5. less effect on cognitive function than PHT
6. hematological toxicity: rare. May be serious → agranulocytosis & aplastic anemia
7. Stevens-Johnson syndrome
8. SIADH
9. hepatitis (occasionally fatal) reported

oxcarbazepine (Trileptal®) DRUG INFO

Very similar efficacy profile to carbamazepine with the following differences:

1. there is no autoinduction (C-P450 is not involved in metabolism) and therefore minimal drug-drug interactions
2. no blood testing is required since:
   A. there is no liver toxicity
   B. there is no hematologic toxicity
   C. there is no need to check drug levels
3. dosing is BID

4. kinetics are linear
5. more expensive

Dose

Rx: starting dose for pain control is 150 mg PO BID, for seizures it is 300 mg PO BID. Maximum dose 2400 mg/day total. **Supplied**: 150, 300 & 600 mg scored tablets. 300 mg/5 ml oral suspension.

valproate DRUG INFO

Available as valproic acid (Depakene®) and divalproex sodium (Depakote®).

Indications

Effective in primary GTC. Also useful in ABS with GTC, juvenile myoclonic epilepsy, and partial seizures (not FDA approved for latter). Also FDA approved for migraine prophylaxis. Note: severe GI upset and short half life make valproic acid much less useful than Depakote® (divalproex sodium).

Dose

Adult range: 600-3000 mg/d. **Peds** range: 15-60 mg/kg/d. MDF = q d.

Rx Start at 15 mg/kg/d, increment at 1 wk intervals by 5-10 mg/kg/d. Max recommended adult dose: 60 mg/kg/d. If daily dose > 250 mg is required, it should be divided. **Supplied**: Oral: capsules 250 mg. Syrup 250 mg/5-ml. **Depakote**® (enteric coated) tabs: 125, 250, & 500 mg; sprinkle capsules[125] mg. IV: **Depacon**® for I.V. injection 500 mg/5 ml vial.

Pharmacokinetics

$t_{1/2}$ (half-life)	t_{PEAK} (peak serum levels)	t_{SS} (steady state)	$t_{D/C}$ (discontinue)	Therapeutic level (µg/ml)
8-20 hrs	(uncoated) 1-4 hrs	2-4 days	4 wks	50-100

Valproic acid **(VA)** is 90% protein bound. ASA displaces VA from serum proteins.

Side effects

Serious side effects are rare. Pancreatitis has been reported. Fatal liver failure has occurred especially if age < 2 yrs and in combination with other AEDs. Teratogenic (*see Contraindications* below). Drowsiness (temporary), minimal cognitive deficits, N/V (minimized with Depakote), liver dysfunction, hyperammonemia (even without liver dysfunction), weight gain, mild hair loss, tremor (dose related; similar to benign familial tremor; if severe and valproic acid is absolutely necessary, the tremor may be treated with beta blockers). May interfere with platelet function, caution with surgery on these patients.

CONTRAINDICATIONS

✖ Pregnancy: causes neural tube defects **(NTD)** in ≈ 1-2% of patients[72]. Since a correlation between peak VA levels and the risk of NTDs has been found, if VA must be used, some experts recommend changing from BID to TID dosing. ✖ Patients ≤ 2 yrs age (risk of hepatotoxicity).

phenobarbital **DRUG INFO**

INDICATIONS

Used as alternative in GTC and partial (not DOC). Had been DOC for febrile seizures, dubious benefit[47]. About as effective as PHT, but very sedating. Also used for status epilepticus (*see page 406*).

DOSE

Same dose PO, IV, or IM. MDF = q d[73, 74]. Start slowly to minimize sedation.

Rx **Adult** loading: 20 mg/kg slow IV (administer at rate < 100 mg/min). Maintenance: 30-250 mg/d (usually divided BID-TID). **Peds** loading: 15-20 mg/kg. Maintenance: 2-6 mg/kg/d (usually divided BID). **SUPPLIED**: tabs 15 mg, 30 mg, 60 mg, 100 mg; elixir 20 mg/5-ml.

PHARMACOKINETICS

$t_{1/2}$ (half-life)	t_{PEAK} (peak levels)	t_{SS} (steady state)	$t_{D/C}$ (discontinue)	Therapeutic level
adult: 5 d (range: 50-160 hrs) peds: 30-70 hrs	PO & IM: 1-6 hrs	16-21 days (may take up to 30 days)	≈ 6-8 wks (reduce ≈ 25% per week)	15-30 µg/ml

Phenobarbital is a potent inducer of hepatic enzymes that metabolize other AEDs.

Side effects

Cognitive impairment (may be subtle and may outlast administration of the drug by at least several months[47]), thus avoid in peds; sedation; paradoxical hyperactivity (especially in peds); may cause hemorrhage in newborn if mother is on phenobarbital.

primidone (Mysoline®) DRUG INFO

Indications

Same as phenobarbital (not DOC). NB: when used in combination therapy, low doses (50-125 mg/day) may add significant seizure control to the primary AED with few side effects.

Dose

Rx **Adult**: 250-1500 mg/d. **Peds**: 15-30 mg/kg/d; MDF = BID.

Start at 125 mg/d **x** 1 wk, and inc. slowly to avoid sedation. **Supplied**: (oral only): scored tabs 50 mg, 250 mg; suspension 250 mg/5-ml.

Pharmacokinetics

Metabolites include phenylethylmalonamide (PEMA) and phenobarbital. Therefore always check phenobarbital level at same time as primidone level.

$t_{1/2}$ (half-life)	t_{PEAK} (peak levels)	t_{SS} (steady state)	$t_{D/C}$ (discontinue)	Therapeutic level (µg/ml)
Primidone: 4-12 hrs derived phenobarbital: 50-160 hrs	2-5 hrs	up to 30 days	same as phenobarbital	primidone: 1-15 derived phenobarbital: 10-30

Side effects

Same as phenobarbital, plus: loss of libido, rare macrocytic anemia.

ethosuximide (Zarontin®) DRUG INFO

Indications

DOC in ABS.

Dose

***Rx* Adult**: 500-1500 mg/d. **Peds**: 10-40 mg/kg/d; MDF = q d. **Supplied**: oral only; capsules 250 mg; syrup 250 mg/5-ml.

Pharmacokinetics

$t_{1/2}$ (half-life)	t_{PEAK} (peak levels)	t_{SS} (steady state)	Therapeutic level (µg/ml)
adult: 40-70 hrs peds: 20-40 hrs	1-4 hrs	adult: up to 14 days peds: up to 7 days	40-100

Side effects

N/V; lethargy; hiccups; H/A; rarely: eosinophilia, leukopenia, erythema multiforme, Stevens-Johnson syndrome, SLE-like syndrome. Toxic levels → psychotic behavior.

methsuximide (Celontin®) DRUG INFO

Indications

Indicated for absence seizures refractory to other drugs.

Dose

Rx optimum dose must be determined by trial. Start with 300 mg PO q d, increase by 300 mg PRN at weekly intervals up to 1200 mg/d. **Supplied**: 150 & 300 mg capsules.

felbamate (Felbatol®) DRUG INFO

✖ CAUTION: Due to an unacceptably high rate of aplastic anemia and hepatic failure, felbamate **(FBM)** should *not* be used except in those circumstances where the benefit clearly outweighs the risk; then, hematologic consultation is recommended by the manufacturer. See *Side effects* below (also for drug-drug interactions).

FBM is efficacious for monotherapy and adjunctive therapy for partial seizures (complex and secondary generalization), and reduces the frequency of atonic and GTC seizures in Lennox-Gastaut syndrome.

PHARMACOKINETICS

$t_{1/2}$ (half-life)	t_{PEAK} (peak levels)	t_{SS} (steady state)	Therapeutic level
20-23 hrs	1-3 hrs	5-7 days	not established

DOSE

Rx: CAUTION *see above*. Felbamate is <u>not</u> to be used as a first-line drug. Patient or guardian should sign informed consent release. Start with 1200 mg/d divided BID, TID, or QID, and decrease other AEDS by one third. Increase felbamate biweekly in 600 mg increments to usual dose of 1600-3600 mg/d (max: 45 mg/kg/d). Slow down increments and/or reduce other AEDs further if side effects become severe. Administer at upper end of range when used as monotherapy. **SUPPLIED**: (oral only) 400 & 600 mg scored tablets; sus-pension 600 mg/5-ml.

Table 17-10 Effect of felbamate on other AED levels

AED	Change in level	Recommended dosing change
phenytoin	↑ 30-50%	↓ 20-33%
carbamazepine	↓ 30% total ↑ 50-60% epoxide	↓ 20-33%
valproic acid	↑ 25-100%	↓ 33%

SIDE EFFECTS

Felbamate has been associated with aplastic anemia (usually discovered after 5-30 wks of therapy) in ≈ 2-5 cases per million persons per yr, and hepatic failure (some fatal, necessitating baseline and serial LFTs every 1-2 wks). Other side effects: insomnia, anorexia, N/V, H/A. Felbamate is a potent metabolic inhibitor, thus it is necessary to reduce the dose of phenytoin, valproate or carbamazepine when used with felbamate[75] (*see Table 17-10*) (general rule: drop dose by one third).

levetiracetam (Keppra®) DRUG INFO

No identified drug-drug interactions. Less than 10% protein bound. Linear pharmakokinetics, no level monitoring needed.

Indications

Adjunctive therapy for partial onset Sz with secondary generalization in patients 4 years of age and older. Myoclonic seizures (juvenile myoclonic epilepsy). Generalized tonic-clonic.

Dose

Rx start with 500 mg PO BID. Increment by 1000 mg/d q 2 weeks PRN to a maximum of 3000 mg/d. Keppra XR: the same dose of levetiracetam can be converted to Keppra XR for q d dosing.

IV: 500-1500 mg diluted in 100 ml of diluent (LR, D5W, normal saline) infused over 15 minutes BID.

Supplied: 250, 500, 750 & 1000 mg scored film-coated tabs; 100 mg/ml oral solution. Keppra XR (extended release) 500 mg.

IV: 1 vial (5 ml) contains 500 mg.

Side effects

PO or IV: somnolence and fatigue in 15%. Dizziness in 9%. Asthenia 15% and infection 13% (nasopharyngitis and influenza may or may not have been related).

Keppra XR: somnolence 8%, irritability 6%.

clonazepam (Klonopin®) DRUG INFO

A benzodiazepine derivative.

Indications

✖ Not a recommended drug for seizures (*see below*).

Used for myoclonic, atonic, and absence seizures (in absence, less effective than valproate or ethosuximide, and tolerance may develop).

NB: clonazepam usually works very well for several months, and then tends to become less effective, leaving only the sedating effects. Also, many cases have been reported of patients having seizures during withdrawal, including status epilepticus (even in patients with no history of status). Thus, may need to taper this drug over 3-6 months.

DOSE

***Rx* Adult**: start at 1.5 mg/d DIV TID, increase by 0.5-1 mg q 3 d, usual dosage range is 1-12 mg/d (max 20 mg/d); MDF = q d. **Peds**: start at 0.01-0.03 mg/kg/d DIV BID or TID, increase by 0.25-0.5 mg/kg/d q 3 d; usual dosage range is 0.01-0.02 mg/kg/d; MDF = q d. **SUPPLIED**: oral only; scored tabs: 0.5 mg, 1 mg, 2 mg.

PHARMACOKINETICS

$t_{1/2}$ (half-life)	t_{PEAK} (peak levels)	t_{SS} (steady state)	$t_{D/C}$ (discontinue)	Therapeutic level (μg/ml)
20-60 hrs	1-3 hrs	up to 14 days	≈ 3-6 months*	0.013-0.072

* CAUTION: withdrawal seizures are common, *see text* above

SIDE EFFECTS

Ataxia; drowsiness; behavior changes.

zonisamide (Zonegran®) DRUG INFO

INDICATIONS

Adjunctive therapy for partial Sz in adults.

acetazolamide (Diamox®) DRUG INFO

The anti-epileptic effect may be either due to direct inhibition of CNS carbonic anhydrase (also reduces CSF production) or due to the slight CNS acidosis that results.

INDICATIONS

Centricephalic epilepsies (absence, nonfocal seizures). Best results are in absence seizures; however benefit has also been observed in GTC, myoclonic jerk.

SIDE EFFECTS

Do not use in first trimester of pregnancy (may be teratogenic). The diuretic effect causes renal loss of HCO_3 which may lead to an acidotic state with long-

term therapy. A sulfonamide, therefore any typical reaction to this class may occur (anaphylaxis, fever, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis…). Paresthesias: medication should be discontinued.

Dose

***Rx* Adult**: 8-30 mg/kg/d in divided doses (max 1 gm/d, higher doses do not improve control). When given with another AED, the suggested starting dose is 250 mg once daily, and this is gradually increased. **SUPPLIED**: tablets 125, 250 mg. Diamox sequels® are sustained release 500 mg capsules. Sterile cryodessicated powder is also available in 500 mg vials for parenteral (IV) use.

Although developed to be a GABA agonist, it does not interact at any known GABA

gabapentin (Neurontin®) DRUG INFO

receptor. Efficacious for primary generalized seizures and partial seizures (with or without secondary generalization). Ineffective for absence seizures. Very low incidence of known side-effects. No known drug interactions (probably because it is renally excreted). Also used for central pain

Dose

***Rx* Adult**: 300 mg PO **x** 1 day 1; 300 mg BID day 2; 300 mg TID day 3; then increase rapidly up to usual doses of ≈ 800-1800 mg per day. Doses of 1800-3600 may be needed in intractable patients. ✖ Dosage must be reduced in patients with renal insufficiency or on dialysis (see *Eq 3-1*, page 46 to estimate). **SUPPLIED**: 100, 300, 400, 600, 800 mg capsules. 50 mg/ml suspension.

Pharmacokinetics

Gabapentin is not metabolized, and 93% is excreted unchanged renally with plasma clearance directly proportional to creatinine clearance[76]. Does not affect hepatic microsomal enzymes, and does not affect metabolism of other AEDs. Antacids decrease bioavailablilty by ≈ 20%, therefore give gabapentin > 2 hrs after the antacid[77].

$t_{1/2}$ (half-life)	t_{PEAK} (peak levels)	t_{SS} (steady state)	Therapeutic level
5-7 hrs*	2-3 hrs	1-2 days	not established

* with normal renal function

Side effects

Somnolence, dizziness, ataxia, fatigue, nystagmus; all reduce after 2-3 weeks of drug therapy. Increased appetite. Not known to be teratogenic.

lamotrigine (Lamictal®) DRUG INFO

Anticonvulsant effect may be due to presynaptic inhibition of glutamate release[76].

Efficacious as <u>adjunctive</u> therapy for partial seizures (with or without secondary generalization) and Lennox-Gastaut syndrome. Preliminary data suggest it may also be useful as an adjunct for refractory generalized seizures, or as monotherapy for newly diagnosed partial or generalized seizures[78]. Also FDA approved for bipolar disorder.

Side effects

Somnolence, dizziness, diplopia. ✖ Serious rashes requiring hospitalization and discontinuation of therapy have been reported (rash usually begins 2 weeks after initiating therapy and may be severe and potentially life-threatening, including Stevens-Johnson syndrome (more of a concern with simultaneous use of valproate), and rarely, toxic epidermal necrolysis **(TEN)**). Incidence of significant epidermal reaction may be decreased by a slow ramping-up of dosage. May increase seizure frequency in severe myoclonic epilepsy of infancy[79]. Metabolism of lamotrigine is affected by other AEDs.

Dose

***Rx* Adult**: In adults receiving enzyme-inducing AEDs (PHT, CBZ, or phenobarbital), start with 50 mg PO q d **x** 2 wks, then 50 mg BID **x** 2 wks, then ↑ by 100 mg/d q week until the usual maintenance dose of 200-700 mg/d (divided into 2 doses) is reached. For patients on valproic acid **(VA)** alone, the maintenance dose was 100-200 mg/d (divided into 2 doses), and VA levels drop by ≈ 25% within a few weeks of starting lamotrigine. For patients on both enzyme-inducing AEDs <u>and</u> VA, the starting dose is 25 mg PO qod **x** 2 wks, then 25 mg qd **x** 2 wks, then ↑ by 25-50 mg/d q 1-2 wks up to a maintenance of 100-150 mg/d (divided into 2 doses). Instruct patients that rash, fever or lymphadenopathy may herald a serious reaction and that a physician should be contacted immediately. **Peds**: not indicated for use in patients < 16 yrs old due to higher incidence of potentially life-threatening rash in the pediatric population[76].

Supplied: 25, 100, 150 & 200 mg tablets. 2, 5 & 25 mg chewable dispersible tablets.

Pharmacokinetics[78]

$t_{1/2}$ (half-life)	t_{PEAK} (peak levels)	t_{SS} (steady state)	Therapeutic level
24 hrs*	1.5-5 hrs	4-7 days	controversial[121]

* half-life is shortened to ≈ 15 hrs by PHT and CBZ, whereas valproic acid increases it to 59 hrs

vigabatrin DRUG INFO

Indications

Effective in treating partial seizures. Less so for generalized seizures.

Dose

***Rx* Adult**: 1500-3000 mg/d.

topiramate (Topamax®) DRUG INFO

May block voltage-sensitive sodium channels and enhance GABA activity at $GABA_A$ receptors and attenuate some glutamate receptors[76].

Indications[80]

As an oral adjunct to other drugs in treating refractory partial onset seizures.

Dose

***Rx* Adult**: start with 50 mg/d and increase slowly up to 200-400 mg/d[81], with no significant benefit noted at dosages > 600 mg/d[82]. **Supplied**: 25, 100, & 200 mg tabs.

Pharmacokinetics

30% is metabolized in the liver, the rest is excreted unchanged in the urine.

$t_{1/2}$ (half-life)	t_{SS} (steady state)	Therapeutic level

19-25 hrs	5-7 days	not established

SIDE EFFECTS

May increase phenytoin concentration by up to 25%. Levels of topiramate are reduced by other AEDs (phenytoin, carbamazepine, valproic acid and possibly others).

Cognitive impairment (word finding difficulty, problems with concentration…), weight loss, dizziness, ataxia, diplopia, paresthesias, nervousness and confusion have been troublesome. ≈ 1.5% incidence of renal stones which usually pass spontaneously[76]

Oligohidrosis (reduced sweating) and hyperthermia, primarily in children in association with elevated environmental temperatures and/or vigorous physical activity.

tiagabine (Gabitril®) **DRUG INFO**

A GABA uptake inhibitor, with cognitive problems of a similar frequency to that with topiramate[83].

Rx **Adult**: start with 4 mg/d, increase weekly by 4-8 mg to a maximum of 32-56 mg (divided BID to QID). **SUPPLIED**: 4, 12, 16 & 20 mg tablets.

lacosamide (Vimpat®) **DRUG INFO**

Enhances slow inactivation of voltage gated sodium channels, affecting only neurons that are depolarized of active over a prolonged period (as in a seizure).

INDICATIONS

Partial onset seizures. Painful diabetic neuropathy.

DOSE

Rx **Adult**: 200-400 mg. **SUPPLIED**: 50, 100, 150 & 200 mg tabs. 10 mg/ml IV solution.

17.4.3.1. Withdrawal of antiepileptic drugs

Most seizure recurrences develop during the first 6 months after AED withdrawal[84].

Indications for AED withdrawal

There is no agreement on how long a patient should be seizure-free before withdrawal of anticonvulsants, nor is there agreement on the prognostic value of EEGs and on the best time period over which to withdraw AEDs.

The following is based on a study of 92 patients with idiopathic epilepsy, who had been free of seizures for two years[85]. Generalization, e.g. to posttraumatic seizures, may not be appropriate. Taper was by 1 "unit" q 2 weeks (where a unit is defined as 200 mg for CBZ or valproic acid, or 100 mg for PHT). Follow-up: mean = 26 mos (range: 6-62).

Table 17-11 EEG class and seizure relapse rate

Class	– – EEG description – –		Re-lapse rate	No. of relapses/ patients at risk
	Before treatment	Before with-drawal		
1	normal	normal	34%	11/31
2	abnormal	normal	11%	4/35
3	abnormal	improved	50%	2/4
4	abnormal	unchanged	74%	14/19

31 patients (34%) relapsed, with the average time to relapse being 8 mos (range: 1-36). Using actuarial methods, the risk for recurrence is 5.9%/month for 3 months, then 2.7%/month for 3 months, then 0.5%/month for 3 months. Factors found to affect the likelihood of relapse include:

1. seizure type: 37% relapse rate for generalized seizures; 16% for complex or simple partial; 54% for complex partial with secondary generalization
2. number of seizures before control attained: those with ≥ 100 seizures before control had statistically significant higher relapse rate
3. the number of drugs that had to be tried before single drug therapy successfully controlled seizures: 29% if 1st drug worked, 40% if a change to a 2nd drug was needed, and 80% if a change to a 3rd drug was required
4. EEG class (*see Table 17-11*): class 4 had worst prognosis for relapse. Epileptiform discharges on EEG serves to discourage AED withdrawal[86]

In a larger randomized study[87], the most important factors identified to predict freedom from recurrent seizures were:

1. longer seizure-free period
2. use of only one AED (vs. multiple AEDs)

3. seizures other than tonic-clonic seizures

WITHDRAWAL TIMES

The recommended withdrawal times in *Table 17-12* should be used only as guide-lines.

Table 17-12 Recommended AED withdrawal times

AED	Recommended withdrawal period
phenytoin, valproic acid, carbamazepine	2-4 weeks
phenobarbital	6-8 weeks (25% per week)
clonazepam	3-6 months (see CAUTION on page 415)

17.4.3.2. Pregnancy and antiepileptic drugs

Women of childbearing potential with epilepsy should undergo counseling regarding pregnancy[88].

BIRTH CONTROL

AEDs that induce liver microsomal cytochrome P_{450} enzymes (*see Table 17-13*) increase the failure rate of oral contraceptives up to fourfold[90]. Patients desiring to use BCPs should employ barrier contraceptive measures until ovulation is consistently suppressed, and they should watch for breakthrough bleeding which may indicate a need for a change in the hormone dosage[84]. Non-oral hormonal contraceptives (e.g. levonorgestrel implant (Nor-plant®)) circumvents first pass liver degradation but should combined with a barrier method because of declining effectiveness with time.

Table 17-13 Effect of AEDs on liver cytochrome P_{450}*

Inducers	Noninducers
carbamazepine phenobarbital phenytoin felbamate primidone	valproic acid benzodiazepines gabapentin lamotrigine

* references[84, 89]

COMPLICATIONS DURING PREGNANCY

Women with epilepsy have more complications with pregnancy than mothers without epilepsy, but > 90% of pregnancies have a favorable outcome[84].

There is an increase in the number of gravid seizures in ≈ 17% (reported range: 17-30%) of epileptic women, which may be due to noncompliance or to changes of free drug levels of AEDs during pregnancy (*see Table 17-14*). Isolated seizures can occasionally be deleterious, but usually cause no problem. Status epilepticus poses serious risk to mother and fetus during pregnancy and should be treated aggressively.

There is also a slightly increased risk of toxemia (HTN of pregnancy) and fetal loss.

Table 17-14 Changes in free AED levels during pregnancy[91]

Drug	Change
carbamazepine	↓ 11%
phenobarbital	↓ 50%
phenytoin	↓ 31%
valproic acid	↑ 25%

BIRTH DEFECTS

The incidence of fetal malformations in offspring of patients with a known seizure disorder is ≈ 4-5%, or approximately double that of the general population[92]. The degree to which this is due to the use of AEDs vs. genetic and environmental factors is unknown. All AEDs have the potential to cause deleterious effects on the infant. Polytherapy is associated with an increased risk over monotherapy in a more than additive manner.

Generally, the risk of seizures (with possible concomitant maternal and fetal hypoxia and acidosis) is felt to outweigh the teratogenic risk of most AEDs, but this must be evaluated on a case-by-case basis. Occasionally patients may be weaned off AEDs.

Specific drugs

Carbamazepine **(CBZ)** produced an increased incidence of "minor" malformations (but not of "major" malformations) in one study[93] (this study may have had methodologic problems), and may increase the incidence of neural tube defects **(NTD)**[94]. In utero exposure to phenytoin may lead to the fetal hydantoin syndrome[68, 95] and a child with an IQ lower by ≈ 10 points[96]. Phenobarbital produced the highest incidence of major malformations (9.1%) in one prospective study[97] and was also associated with most of the increase in fetal

death or anomalies in another study[98]. Valproate **(VA)** causes the highest incidence of NTD (1-2%[72]), which can be detected with amniocentesis and allow an abortion if desired. TID dosing may reduce the risk of NTD (*see page 413*). Benzodiazepines given shortly before delivery can produce the "floppy infant syndrome"[99]. Similar effects may occur with other sedating AEDs such as phenobarbital.

Drug recommendations

A general consensus is that for most women of childbearing potential who require AEDs, that monotherapy with the lowest dose of CBZ that is effective is the method of choice if the seizure disorder is responsive to it[100]. If ineffective, then monotherapy with valproic acid (with TID dosing) is currently the recommended second choice. Folate supplementation (after confirming normal B_{12} levels, *see page 1187*) should be used in all.

17.5. Seizure surgery

20% of patients continue to have seizures even with AEDs. Many of these patients may be candidates for surgical procedures to control their seizures[6].

INDICATIONS

Seizure disorder must be severe, medically refractory with satisfactory trials of tolerable medication for at least ≈ 1 year, and disabling to the patient. Medically **refractory** is usually considered two attempts of high-dose monotherapy with two distinct AEDs, and one attempt at polytherapy.

The three general categories of patients suitable for seizure surgery have[101]:

1. partial seizures
   A. temporal origin: the largest group of surgical candidates (especially mesial temporal epilepsy which is often medically refractory)
   B. extratemporal origin
2. secondarily generalized seizures: e.g. Lennox-Gastaut
3. unilateral, multifocal epilepsy associated with infantile hemiplegia syndrome

EVALUATION

All patients should undergo imaging study to rule out neoplasm, AVM, etc. Noninvasive techniques allow localization in the majority of cases.

NONINVASIVE TECHNIQUES

MRI

The imaging modality of choice. Extremely good for detecting hippocampal asymmetry of mesial temporal sclerosis that may produce complex partial seizures **(CPS)**[102].

CAT SCAN

A seizure focus may enhance with IV contrast shortly following a seizure. Subtle enhancement may be present on the side of the focus on interictal CT scan[103].

VIDEO-EEG MONITORING

Most centers perform pre-operative long-term inpatient video-EEG monitoring to correlate the clinically disabling seizure with appropriate electrical abnormalities and possibly to identify the seizure focus.

PET SCAN (POSITRON EMISSION TOMOGRAPHY)

Interictal PET scan using fluorine-18 deoxyglucose (18FDG) shows hypometabolism lateralized to the side of temporal lobe focus in 70% of patients with medically refractory CPS (does not show actual site of origin). Useful when MRI and EEG cannot localize.

SPECT SCAN (SINGLE PHOTON EMISSION TOMOGRAPHY)

Used to demonstrate increased blood flow during a seizure to help localize site of onset. [99m] Technetium (Tc) hexamethyl-propylene-amine-oxime (HMPAO) is usually administered immediately after onset of seizure, and the scan may be obtained within several hours[104].

MILDLY INVASIVE TECHNIQUES

WADA TEST[105]

AKA intracarotid amytal test. Localizes dominant hemisphere (side of language function) and assesses ability of hemisphere without lesion to maintain memory when isolated. Usually reserved for candidates for large resections[106].

Start with angiogram to assess cross flow and to R/O persistent trigeminal artery (*see page 107*). Significant cross-flow is a relative contraindication to anesthetizing the side of dominant supply (patient goes to sleep).

Wada test may be grossly inaccurate with high flow AVM. Also, portions of hippocampus may be supplied by posterior circulation (not anesthetized by ICA injection).

EEG monitoring is usually performed during the test when it is being done for seizure surgery. Patient will show delta waves during deepest level of anesthesia.

Technique

- instruct patient as to what is expected
- catheterize ICA: usually start on side of lesion
- have patient hold contralateral arm in air, and instruct them to hold it there
- inject 100-125 mg sodium amobarbital (Amytal®) rapidly into internal carotid artery (effect starts almost instantaneously, begins to subside after ≈ 8 minutes (may subside in ≈ 2 minutes with AVM where flow rates are high))
- determine adequacy of injection by assessing motor function in elevated arm (should be ≈ flaccid)
- assess language skills by showing patient pictures of objects and ask them to name each one out loud and remember each one
- assess memory function by asking patient to name as many of the pictures as they can ≈ 15 minutes after test: if they have difficulty, ask them to pick out pictures from a group that contains additional ones not shown to patient
- repeat procedure on other side (use lower Amytal doses with each subsequent injection)

SURGICAL TECHNIQUES

EEG OBTAINED WITH INVASIVE ELECTRODES

Risk of infection with depth electrodes[106]: 2-10%.

Surface strip electrodes may be placed through a burr hole.

Depth electrodes may be placed stereotactically. Temporal depth electrodes

may be helpful for CPS, usually to determine the laterality of the mesiotemporal source of seizure. Frontal depth electrodes are also sometimes used. 2-3% risk of intracerebral hemorrhage[106].

Subdural grid electrodes are placed with a craniotomy. These sometimes may allow sufficient mapping to permit surgery under general anesthesia without need for intraoperative mapping under local anesthesia (helpful in children or in the mentally retarded).

SURGICAL CONSIDERATIONS

Three basic types of procedure: resections, disconnections and stimulation[A]:

1. resections
   A. resection of epileptic focus: higher chance of completely controlling seizures. Performed in noneloquent brain. Seizures must have focal onset (resection not encouraged if multifocal onset). Includes:
      1. anterior temporal lobectomy: *see below*
      2. amygdalo-hippocampectomy
      3. neocortical resections: especially with neuronal migration abnormalities
   B. resection of lesion in secondary epilepsy (e.g. tumor, AVM, cavernous malformation[107]…). In most cases the seizure focus is in or near the lesion, but some structural lesions are not responsible for the seizures. For seizure foci within the temporal lobe, seizure control is better when lesionectomy is accompanied by amygdalo-hippocampectomy[108]
2. disconnections: used when eloquent brain is involved, or to separate the electrical activity of the two cerebral hemispheres
   A. section of corpus callosum (callosotomy): when drop attacks are the most disabling seizure type or for multiple bilateral foci (*see below*)
   B. hemispherectomy: for unilateral seizures with widespread hemispheric lesions and profound contralateral neurologic deficit. If any cortex is left, must make sure it is functionally deafferented (disconnected)
      1. anatomic hemispherectomy
      2. functional hemispherectomy: preservation of the basal ganglia isolates the abnormal side with ≈ 80% seizure control rate (similar to anatomic hemispherectomy, but with lower complication rate).
   C. multiple subpial transection[109]: for partial seizure originating in eloquent cortical areas. The cortex is transected at 5 mm intervals, thus

interrupting the horizontal spread of the seizure while sparing the vertically oriented functional fibers

3. stimulation
   A. vagal nerve stimulation: *see page 424*
   B. deep brain stimulation (DBS)
      1. centromedian nucleus of the thalamus[110]: better for generalized tonic-clonic seizures
      2. bilateral anterior nucleus of the thalamus (report of 5 patients[111], and the recent “SANTE” trial[112]): for partial seizures
      3. hippocampus[110]: for partial seizures

A. all of the listed procedures are for <u>refractory</u> seizures. For the definition of refractory, *see page 420*

ANESTHETIC CONSIDERATIONS

If intraoperative electrocorticography is to be performed:

- under local anesthesia: the only anesthetic agents that may be used are narcotics (usually fentanyl) and droperidol
- under general anesthesia: <u>avoid</u> benzodiazepines and barbiturates

INTRAOPERATIVE ELECTROCORTICOGRAPHY ***(ECOG)***

May be performed with surface matrix that includes superior temporal gyrus and inferior frontal gyrus. Depth electrodes in the amygdala (3 cm from temporal tip) and hippocampus (5 cm from temporal tip) may also be used.

Methohexital (Brevitol®) may be given to try to provoke a seizure: observe for ↓ fast activity in suspected focus.

INTRAOPERATIVE CORTICAL MAPPING

For techniques of cortical mapping, *see page 150*.

CORPUS CALLOSOTOMY

Partial or total section may be most effective for generalized major motor seizures. Of little benefit for simple or complex seizures. Benefit has been supported for:

1. frequent episodes of <u>atonic seizures</u> (“drop attacks”) where loss of postural tone → falls and injuries[113] (70% reduction with callosotomy)

2. possibly for generalized seizure disorder with unilateral hemisphere damage (e.g. infantile hemiplegia syndrome); hemicortical resection may be better for this type, whereas callosotomy may promote partial seizures.

   Note: a "functional hemispherectomy" is recommended over "anatomically complete" hemispherectomy to reduce morbidity and mortality[101]

3. some patients with generalized seizures without identifiable, resectable focus

Division of the anterior two thirds of the corpus callosum **(CC)** (minimizes the risk of disconnection syndrome, *see below*) may be advantageous over complete callosotomy (controversial). Some advocate sectioning the CC with intraoperative EEG until the typical bisynchronous discharges that are usually seen become asynchronous[114]. No need to section anterior commissure. Can usually be performed via a bifrontal craniotomy utilizing a bicoronal skin incision.

May produce post-op ↓ verbalization or akinetic mutism that usually resolves in weeks. ✖ Contraindication: major behavioral and/or language deficits may occur even with partial division in patients with speech and dominant handedness located in opposite hemispheres ("crossed dominance"). Thus, Wada test is recommended in all left handed patients.

MRI sagittal cuts are superb for assessing extent of division of the CC[115].

DISCONNECTION SYNDROME

In a patient with a dominant left hemisphere, consists of left tactile anomia, left sided dyspraxia (may resemble hemiparesis), pseudohemianopsia, right sided anomia for smell, impaired spatial synthesis of right hand resulting in difficulty copying complex figures, decreased spontaneity of speech, incontinence.

More common with larger surgical sections of the CC. Risk is less if the anterior commissure is spared. Patients usually adapt after 2-3 months, with final function normal for most daily activities (deficits may show up on neuropsychological testing).

TEMPORAL LOBECTOMY

80% of patients with medically intractable seizures with demonstrable focus have foci in anterior temporal lobe. Most patients have neuronal loss and gliosis of mesial temporal structures. Thus, a standard resection of temporal tip (often with amygdalo-hippocampectomy) may be performed.

Limits of resection (without significant neurologic deficit)

Note that these values are generally considered safe, however, variations occur from patient to patient and only intraoperative mapping can reliably determine the location of language centers[116]. Some centers spare the superior temporal gyrus[117]. The following measurements are made along the middle temporal gyrus

- dominant temporal lobe: up to 4-5 cm may be removed. Over-resection may injure speech centers, which cannot be reliably localized visually
- non-dominant temporal lobe: 6-7 cm may be resected. Slight over-resection may → partial contralateral upper quadrant homonymous hemianopsia; resection of 8-9 cm → complete quadrantanopsia

Alternatively, intraoperative electrocorticography may be used to guide resection of electrically abnormal areas.

Resection should be performed in subpial plane to prevent injury to MCA branches.

AMYGDALO-HIPPOCAMPECTOMY

The amygdala lies in the roof of the anterior temporal horn of the lateral ventricle.

Two basic approaches:

1. transcortical: image guidance is very helpful
   A. Niemeyer approach[118]: 2-3 cm longitudinal cortical incision through the middle temporal gyrus centered at a point ≈ 4 cm posterior to the temporal tip
   B. approach through the anterior superior temporal gyrus
2. transsylvian: approach advocated by Yasargil. More restrictive and greater risk of injury to M1 portion of MCA within sylvian fissure

Complications: vascular injury is the most significant risk.

RISKS OF SEIZURE SURGERY

Major risks are related to[119]:

1. removal of essential areas of cortex
2. injury to medullary core underlying cortical resection (projection fibers, association fibers, and/or commissural fibers): the most common deficit

after temporal lobectomy is a contralateral (homonymous) superior quadrantanopsia (so-called "pie-in-the-sky" defect, due to an injury to Meyer's loop wherein the fibers for the superior visual field of the optic radiation take a slight rostral "detour" towards the temporal tip)

3. injury to vessels in area of resection → ischemic damage to areas supplied: especially sylvian branches during temporal lobectomy or ACA branches with corpus callosotomy
4. injury to nearby cranial nerves: especially third nerve during hippocampectomy where it lies medial to tentorium

PERIOPERATIVE MANAGEMENT FOR SEIZURE SURGERY

Management during evaluation:

During period when AEDs are being tapered, patient should be observed at all times (for patients not in ICU, a 24 hour-a-day sitter is required).

PRE-OP ORDERS (EPILEPTIC SURGERY)

1. taper anticonvulsants, completely D/C 1 day before surgery
2. 10 mg Decadron® PO hs before surgery, repeat PO or IV on AM of surgery
3. <u>if seizures develop</u>: phenobarbital 130 mg IV (@ < 100 mg/min)

POST-OP ORDERS (EPILEPTIC SURGERY)

1. for seizures in the immediate post-op period ("honeymoon seizures;"), not necessary to treat only one brief generalized seizure, otherwise load appropriately with phenytoin or phenobarbital;
2. continue 4 mg dexamethasone (Decadron®) PO q 6 hrs **x** <u>1 wk</u>, then taper over next week (essential to maintain for full week)
3. anticonvulsants are continued **x** 1-2 years even if no post-op seizures occur
4. before discharge:
   A. neuropsychiatric evaluation
   B. serum anticonvulsant level
   C. EEG

OUTCOME WITH RESECTION OF SEIZURE FOCUS

The greatest effect of seizure surgery is <u>reduction of seizure frequency</u>[117], however, any surgical procedure may fail to have a beneficial effect.

Seizure control is usually assessed at 1,3 & 6 most post op, and then annually. A post-op MRI is usually obtained at 3 most post-op to assess extent of surgical resection. Most patients take anti-epileptic drugs **(AEDs)** for 2 years post-op, and then may be discontinued in those free of seizures.

Recurrent seizures: although late seizures may occur, 90% of seizures that recur do so within 2 years.

2 years post-op in patients maintained on AEDs: 50% are seizure-free, and 80% have over 50% reduction of seizure frequency.

For temporal lobectomies in the dominant hemisphere without intraoperative monitoring, there is a 6% risk of mild dysphasia. Significant memory deficits occur in ≈ 2%.

VAGAL NERVE STIMULATION (VNS)

Electrodes wrapped around the vagus nerve in the neck are connected to an implanted programmable generator to stimulate the nerve to reduce seizure frequency.

As is also true with many AEDs, the mechanism of action is not well understood.

Indications: Although it has been used (off label) for treatment resistant depression and other psychiatric conditions, the FDA approved indication is for adjunctive therapy for patients > 12 years old with partial onset seizures refractory to medical treatment.

Outcome: In a 12 year retrospective review of VNS in 12 patients[120], mean seizure frequency decreased by 26% at 1 year, by 30% at 5 years, and by 52% after 12 years.

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18. Spine & spinal cord

18.1. Low back pain and radiculopathy

Key concepts[1]:

- low back pain is common, and in ≈ 85% of cases, no specific diagnosis can be made
- initial assessment is geared to detecting "red flags" (indicating potentially serious pathology), and in the absence of these, imaging studies and further testing of patients is usually not helpful during the first 4 weeks of low back symptoms
- relief of discomfort is usually best achieved with nonprescription pain meds and/or spinal manipulation
- while activities may need to be modified, bed rest beyond 4 days may be more harmful than helpful, and patients are encouraged to return to work or their normal daily activities as soon as possible
- 89-90% of patients with low back problems will improve within 1 month even without treatment (including patients with sciatica from disc herniation)

Low back pain **(LBP)** is extremely prevalent, and is the second most common reason for people to seek medical attention[2]. LBP accounts for ≈ 15% of all sick leave from work, and is the most common cause of disability for persons < 45 yrs age[3]. Estimates of lifetime prevalence range from 60-90%, and the annual incidence is 5%[4]. Only 1% of patients will have nerve-root symptoms, and only 1-3% have lumbar disc herniation. The prognosis for most cases of LBP is good, and improvement usually occurs with little or no medical intervention.

DEFINITIONS/CLASSIFICATIONS

radiculopathy	dysfunction of a nerve root (signs and symptoms may include: pain in the distribution of that nerve root, dermatomal sensory disturbances, weakness of muscles innervated by

	that nerve root, and hypoactive muscle stretch reflexes of the same muscles)
mechanical low back pain	AKA "musculoskeletal" back pain (both non-specific terms). The most common form of low back pain. May result from strain of the paraspinal muscles and/or ligaments, irritation of facet joints… Excludes anatomically identifiable causes (e.g. tumor, disc herniation…)

INTERVERTEBRAL DISC

The function of the intervertebral disc is to permit stable motion of the spine while supporting and distributing loads under movement.

Anatomy

Anulus fibrosus (anulus may alternatively be spelled annulus, but fibrosus is the only correct spelling and is distinct from *fibrosis*)[5]: the multilaminated ligament that encompasses the periphery of the disc space. Attaches to the end-plate cartilage and ring apophyseal bone. Blends centrally with the nucleus pulposus.

Nucleus pulposus: the central portion of the disc. A remnant of the notocord.

Capsule[5]: combined fibers of the anulus fibrosus and the posterior longitudinal ligament (this term is useful because these 2 structures may not be distinguishable on imaging studies).

NOMENCLATURE FOR DISC PATHOLOGY

Historically, the terminology has been contentious and nonstandardized. Many diagnostic labels are used inconsistently (e.g. spondylosis, sprain, strain, musculoskeletal pain, myofascial pain…). A subset of nomenclature proposed by a task force[5] is shown in *Table 18-1*, which is useful primarily for consistent terminology related to radiographic reports, research….

Degenerated disc: some reports indicate that these can cause radicular pain possibly by an inflammatory mechanism[6], but this is not universally accepted.

Vacuum disc: gas in the disc space (empty space on imaging), usually indicates disc degeneration, <u>not</u> infection.

Non-Standard terms

Included for completeness, but are <u>not</u> recommended because they may be confusing or ambiguous[5].

Contained herniation[5]: displaced disc tissue that is entirely contained within an uninterrupted (but possibly distended) anulus or capsule (*see page 428*

for definition of *capsule*). It may be difficult to distinguish this on currently available imaging studies from an uncontained herniation which is underneath the posterior longitudinal ligament.

Ruptured disc: colloquial term usually intended to be equivalent to herniated disc.

Table 18-1 Nomenclature for lumbar disc pathology[5]

Term	Description
anular tears AKA anular fissures	separations between anular fibers, avulsions of fibers from their VB insertions, or breaks through fibers that extend radially, transversely, or concentrically
degeneration	desiccation, fibrosis, narrowing of the disc space, diffuse bulging of the anulus beyond the disc space, extensive fissuring (numerous anular tears), mucinous degeneration of the anulus, defects & sclerosis of end-plates, & osteophytes at the vertebral apophyses
degenerative disc disease	clinical syndrome of symptoms related to degenerative changes in the intervertebral disc (described above), also often considered to encompass degenerative changes *outside* the disc as well
bulging disc	generalized displacement of disc material (arbitrarily defined as > 50% or 180°) beyond the peripheral limits of the disc space*. Not considered a form of herniation. May be a normal finding, not usually symptomatic
herniation	localized displacement of disc material (< 50% or 180°) beyond the limits of the intervertebral disc space*
	focal: < 25% of the disc circumference
	broad-based: 25-50% of the disc circumference
	protrusion: the fragment does not have a "neck" that is narrower than the fragment in any dimension
	extrusion: the fragment has a "neck" that is narrower than the fragment in at least 1 dimension. 2 subtypes A. **sequestration**: the fragment has lost continuity with the disc of origin (AKA **free fragment**) B. **migration**: the fragment is displaced away from the site of extrusion, regardless of whether sequestered or not
	intravertebral herniation (AKA **Schmorl's node**): disc herniates in the cranio-caudal direction through the cartilaginous end-plate into the VB (*see page 455*)

* intervertebral disc space: bounded by VB endplates in the craniocaudal dimension, and by the outer edges of the vertebral ring apophyses (exclusive of osteophytes) in the peripheral direction

Recommended classification

It is recommended[1] that acute back problems be classified into one of the 3 categories shown in *Table 18-2* based on the history and physical exam (see

Initial assessment of the patient with back pain below). Further evaluation, treatment, and even some information regarding prognosis can be based on this simple classification. A major goal is to detect “red flags” that may indicate potentially serious spinal or nonspinal pathology (*see page 432*).

Table 18-2 AHCPR classification of back problems

Clinical category	Description
potentially serious spinal condition	includes spinal tumor, infection, fracture, or cauda equina syndrome (*see text*)
sciatica	pain along the course of the sciatic nerve, usually resulting from nerve root compromise
nonspecific back symptoms	symptoms occurring primarily in the back that suggest neither nerve root compromise nor a serious underlying condition

NOMENCLATURE FOR SPINE PATHOLOGY OUTSIDE THE DISC

Vertebral body marrow changes:

Associated with degenerative or inflammatory changes. **Modic’s classification**[7] of MRI characteristics is shown in *Table 18-3*.

Kyphosis: Focal kyphosis across a fracture is measured using the **Cobb angle**: the angle between two lines, one drawn parallel to the superior endplate of the VB one level above the injured VB, the other line parallel to the inferior endplate of the VB one level below (showed the best overall intraobserver and interobserver reliability[8]).

Table 18-3 Modic’s classification

Modic Type	Intensity changes		Description	
	T1WI	T2WI		
1*	↓	↑	bone marrow edema associated with acute or subacute inflammation	
2	↑	iso or ↑	chronic changes	replacement of bone marrow by fat
3	↓	↓		reactive osteosclerosis

* Type 1 may respond to fusion, *see page 440*

Scoliosis: Named for the side of the <u>convexity</u> of the curvature (i.e. dextroscoliosis = convex to right, levoscoliosis = convex to left). **Cobb angle**: may also be used (using the superior endplate of the uppermost vertebra

involved and the inferior endplate of the lowest vertebra involved). To make the lines meet within the borders of the film, it is some-times helpful to draw perpendiculars to these lines and measure the angles between those (*see Figure 18-1*).

DISABILITY, PAIN AND OUTCOME DETERMINATIONS

Disability scales for low back pain have been developed to assess outcomes for research purposes. Some widely used measures include:

1. visual analogue scale: used for any type of pain. The patient is asked to mark their pain level on a line divided into segments with sequential labels 0 (no pain) to 10 (the worst pain)
2. **Oswestry disability index (ODI)**[9]: a categorical ordinal scale that is used for low back pain. There are 4 English versions in wide use[10], version 2.011 is recommended[10]. It consists 10 questions related to activities of daily living. Each item is scored 0-5 (5 being the most disability) and the total is multiplied by 2% to obtain the final score (range: 0-100%). The interpretation of the final score is shown in *Table 18-4*. A score > 45% is essentially completely disabled. A score in the teens is very functional
3. Short Form 36 (SF36)[13]
4. Roland–Morris disability questionnaire[12]

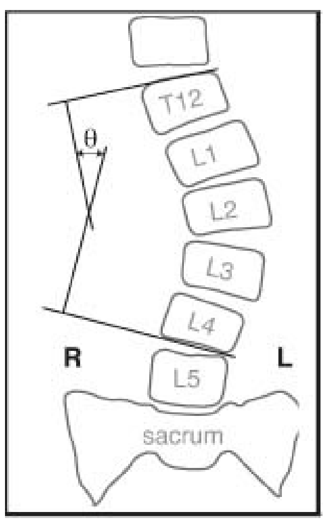

Figure 18-1 Cobb angle AP schematic showing levoscoliosis with Cobb angle?

Table 18-4 Oswestry disability index score

Score	Interpretation
0-20%	minimal disability: can cope with most daily activities

21-40%	moderate disability: pain and difficulty with sitting, lifting & standing. The patient may be disabled from work
41-60%	severe disability: pain is the main problem, but other areas are affected
61-80%	crippled: back pain impinges on all aspects of the patient's life
81-100%	these patients are either bed-bound or else are exaggerating their symptoms

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of low back pain (*see Low back pain*, page 1192) overlaps with that of myelopathy. In ≈ 85% of cases of LBP no specific diagnosis can be made[14].

INITIAL ASSESSMENT OF THE PATIENT WITH BACK PAIN

Initial assessment consists of a history and physical exam focused on identifying serious underlying conditions such as: fracture, tumor, infection or cauda equina syndrome. Serious conditions presenting as low back problems are relatively rare.

HISTORY

The following information has been found to be helpful in identifying patients with serious underlying conditions such as cancer and spinal infection[1]. *Table 18-5* shows the sensitivity and specificity.

1. age
2. history of cancer (especially malignancies that are prone to skeletal metastases: prostate, breast, kidney, thyroid, lung)
3. unexplained weight loss
4. immunosuppression: from steroids, organ transplant medication, or HIV
5. prolonged use of steroids
6. duration of symptoms
7. responsiveness to previous therapy
8. pain that is worse at rest
9. history of skin infection: especially furuncle
10. history of IV drug abuse
11. UTI or other infection

12. pain radiating below the knee
13. persistent numbness or weakness in the legs
14. history of significant trauma. In a young patient: MVA, a fall from a height, or a direct blow to the back. In an older patient: minor falls, heavy lifting or even severe coughing can cause a fracture especially in the presence of osteoporosis
15. findings consistent with cauda equina syndrome (*see page 446*):
    A. bladder dysfunction (usually urinary retention, or over-flow incontinence) or fecal incontinence
    B. saddle anesthesia: *see page 446*
    C. unilateral or bilateral leg weakness or pain
16. psychological and socioeconomic factors may influence the patient's report of symptoms (also *see page 436*), and one should inquire about:
    A. work status
    B. typical job tasks
    C. educational level
    D. pending litigation
    E. worker's compensation or disability issues
    F. failed previous treatments
    G. substance abuse
    H. depression

Table 18-5 Sensitivity and specificity of historical findings in patients with low back problems[1]

Condition	History	Sensitivity	Specificity
cancer	age ≥ 50 yrs	0.77	0.71
	previous Ca	0.31	0.98
	unexplained weight loss	0.15	0.94
	failure to improve after conservative therapy **x** 1 month	0.31	0.90
	any of the above	1.00	0.60
	pain > 1 month	0.50	0.81
spinal osteomyelitis	IV drug abuse, UTI, or skin infection	0.40	NA
compression fracture	age ≥ 50 yrs	0.84	0.61
	age ≥ 70yrs	0.22	0.96
	trauma	0.30	0.85
	steroid use	0.06	0.995
HLD	sciatica	0.95	0.88
spinal stenosis	pseudoclaudication	0.60	NA
	age ≥ 50 yrs	0.90*	0.70
ankylosing spondylitis	positive response to 4 out of 5 of the following	0.23	0.82
	age at onset ≤ 40 yrs	1.00	0.07
	pain not relieved when supine	0.80	0.49
	AM back stiffness	0.64	0.59
	pain ≥ 3 mos duration	0.71	0.54

* estimate

PHYSICAL EXAMINATION

Less helpful than the history in identifying patients who may be harboring conditions such as cancer, but may be more helpful in detecting spinal infections.

1. spinal infection (*see page 376*): findings that suggest this as a possibility (but are also common in patients without infection)
   A. fever: common in epidural abscess and vertebral osteomyelitis, less common in discitis
   B. vertebral tenderness
   C. very limited range of spinal motion
2. findings of possible neurologic compromise: the following physical findings will identify most cases of clinically significant nerve root compromise due to L4-5 or L5-S1 HLD which comprise > 90% of cases of radiculopathy due to HLD (limiting the exam to the following might not

detect the much less common upper lumbar disc herniations, which may be difficult to detect on PE, *see page 453*)

A. dorsiflexion strength of ankle and great toe: weakness suggests L5 and some L4 dysfunction
B. achilles reflex: diminished reflex suggests S1 root dysfunction
C. light touch sensation of the foot:
   1. diminished over medial malleolus and medial foot: suggests L4
   2. diminished over dorsum of foot: suggests L5
   3. diminished over lateral malleolus and lateral foot: suggests S1
D. straight leg raising **(SLR)** (also check for crossed SLR): *see page 443*

"Red flags" in the history and physical exam for low back problems

Based upon the above history and physical exam, the findings in *Table 18-6* would suggest the possibility of a serious underlying condition as the cause of the low back problem. Also, thoracic region pain is relatively uncommon and should raise the index of suspicion.

Further evaluation

For over 95% of patients with acute low back problems, no further testing within the first 4 weeks of symptoms is required[1].

In the absence of any of the "red flag" conditions shown in *Table 18-6*, no further testing is recommended (even for patients suspected of having a HLD) and the treatment is similar for most patients with an acute episode of low back problems.

Simple laboratory tests including CBC and ESR are sufficiently efficacious and inexpensive that they should be obtained when there is a suspicion of back related tumor or infection.

Table 18-6 "Red flags" for patients with low back problems

Condition	Red flags
cancer or infection	1. age > 50 or < 20 yrs 2. history of cancer 3. unexplained weight loss 4. immunosuppression (*see text*) 5. UTI, IV drug abuse, fever or chills 6. back pain not improved with rest
spinal fracture	1. history of significant trauma (*see text*) 2. prolonged use of steroids 3. age > 70 yrs
cauda equina syndrome or severe neurologic compromise	1. acute onset of urinary retention or overflow incontinence

	2. fecal incontinence or loss of anal sphincter tone 3. saddle anesthesia 4. global or progressive weakness in the LEs

FURTHER EVALUATION OF PATIENTS WITH LOW BACK PROBLEMS

Except for those exhibiting "red flags" (*see above*), special diagnostic tests are usually not needed during the first month of symptoms since it is not possible to predict which patients will improve (as most do) and which will not.

TESTS FOR EVIDENCE OF PHYSIOLOGIC DYSFUNCTION

Electrodiagnostics for low back problems: If the diagnosis of radiculopathy seems likely on clinical grounds, electrophysiologic testing is not recommended[1].

1. needle EMG: (*see page 269*) can assess acute and chronic nerve root dysfunction, myelopathy and myopathy, and may be useful for patients with suspicion of other conditions (e.g. neuropathy) or when a reliable strength exam is not possible. Reduced recruitment may be seen within the first several days of onset, however, spontaneous activity (*see page 270*) takes **10-21 days** to develop (∴ less helpful in the first ≈ 3 weeks). Also, not usually helpful with normal muscle strength exam. Accuracy is highly operator dependent and improves with knowledge about imaging studies and clinical information[15]. For findings in radiculopathy, *see page 270*
2. H-reflex (*see page 270*): measures sensory conduction through nerve roots. Correlates with achilles reflex. Use is limited to assessing S1 radiculopathy[16]
3. SSEPs: (*see page 266*) assesses afferent fibers which travel in peripheral nerve and the posterior column of the spinal cord. May be abnormal in conditions affecting the dorsal columns with impaired joint position and proprioception (e.g. cervical spondylotic spinal myelopathy)
4. nerve conduction studies (including NCVs): helps identify acute and chronic entrapment neuropathies that may mimic radiculopathy
5. ✖ not recommended for assessing acute low back problems[1]
   A. F-wave response (*see page 270*): measures motor conduction through nerve roots, used to assess proximal neuropathies
   B. surface EMG: assesses acute and chronic recruitment patterns during static or dynamic tasks using surface (instead of needle) electrodes

Bone scan for low back problems: Description: injection of a - radiolabeled compound (usually technetium-99m) that is taken up by metabolically active bone. A gamma camera localizes regions of uptake. Total radiation dose is ≈ to a set of lumbar spine x-rays[1]. Contraindicated during pregnancy, and breast feeding must be briefly suspended following a bone scan due to presence of radiotracer in the breast milk.

A moderately sensitive test which may be used in evaluating low back pain when spinal tumor[17], infection[18], or occult fracture is suspected from "red flags" (*see Table 18-6*) on history or examination, or results of lab tests or plain x-rays. Not very specific, but may locate occult lesions and help differentiate these conditions from degenerative changes. A positive bone scan suggesting one of these conditions usually must be confirmed by other diagnostic tests or procedures (no studies have compared bone scans to CT or MRI).

Low yield in patients with longstanding low back problems and normal plain x-rays and laboratory tests (especially ESR)[17].

SPECT scans may provide additional information to a bone scan.

Thermography for low back problems: Not recommended[1]. Did not accurately predict absence or presence of nerve root compression seen at surgery[19], and may be positive in a significant percentage of asymptomatic patients[20].

RADIOGRAPHIC EVALUATION

Diagnosing lumbar spinal stenosis or herniated intervertebral disc is usually helpful only in potential surgical candidates[21]. This includes patients with appropriate clinical syndromes who have not responded satisfactorily to adequate non-surgical treatment over a sufficient period of time, and who have no medical contraindications to surgery. Radiologic confirmation of these diagnoses usually requires CT, myelography, MRI, or some combination (*see below*). NB: myelography[22], CT[23], or MRI[24] may also show bulging or herniated lumbar discs **(HLD)** or spinal stenosis in asymptomatic patients (e.g. 24% of asymptomatic patients have herniated discs on MRI and 4% have spinal stenosis; these numbers become 36% and 21% respectively in patients 60-80 years old)[25]. Thus, these tests must be interpreted in light of clinical findings, and the anatomic level and side should correspond to the history, examination, and/or other physiologic data. Diagnostic radiology is of limited benefit as the initial evaluation in the majority of spinal disorders[26].

In the absence of red flags for serious conditions, imaging studies are not

recommended in the first month of symptoms[1]. For patients who have had previous back surgery, MRI with contrast is probably the best test. Myelography (with or without CT) is invasive and has increased risk of complications, and is therefore indicated only in situations where MRI cannot be done or is inadequate, and surgery is anticipated.

Σ

Patients for whom radiographic imaging is recommended are those with:
- suspected *benign* conditions with symptoms of great enough severity to consider surgery persisting beyond 4 weeks, including:
  - back related leg symptoms and clinically specific signs of nerve root compromise
  - a history of neurogenic claudication (*see page 477*) or other finding suggestive of lumbar spinal stenosis
- red flags: physical examination or other test results suggesting other serious conditions affecting the spine (e.g. cauda equina syndrome, fracture, infection, tumor, or other mass lesions or defects)

Recommendations for use of MRI and discography to select patients for fusion are shown in *PRACTICE GUIDELINE 18-1*.

PRACTICE GUIDELINE 18-1 MRI & DISCOGRAPHY FOR PATIENT SELECTION FOR LUMBAR FUSION*

Level II[27]:
- MRI is recommended as the initial diagnostic test
- normal appearing discs on MRI should not be considered for discography or treatment
- lumbar discography should not be used as a stand-alone test
- to consider a disc level for treatment, if discography is used, there should be a concordant pain response† and associated abnormalities on MRI‡

Level III[27]: discography should be reserved for equivocal MRI findings, especially at levels adjacent to unequivocally abnormal levels

* for recommendations on use of facet injections, see *PRACTICE GUIDELINE 18-2*, page 437

† concordant pain response: pain identical or very similar to the patient's usual pain complaints (NB: discography can produce severe LBP in patients with no prior complaints[28, 29])

‡ abnormal disc morphology on MRI: loss of T2WI signal intensity ("black disc"), disc space collapse, Modic changes (*see page 430*), and high-intensity zones (these findings also frequently occur in asymptomatic patients 30)

PLAIN LUMBOSACRAL X-RAYS

Unexpected findings occurred in only 1 in 2500 adults < 50 years age[31].

Diagnosis of surgical conditions of disc herniation and spinal stenosis cannot be made from plain films. Various congenital abnormalities of uncertain significance may be identified (e.g. spina bifida occulta), and evidence of degenerative changes (including osteophytes) are as frequent in symptomatic as in asymptomatic patients. Gonadal radiation is significant. Seldom indicated during pregnancy.

Recommendation

Not recommended for routine evaluation of patients with acute low back problems during the first month of symptoms unless a “red flag” is present (*see below*). Reserve LS x-rays for patients with a likelihood of having spinal malignancy, infection, inflammatory spondylitis, or clinically significant fracture. In these cases, plain x-rays are often just a starting point, and further study (CT, MRI…) may be indicated even if the plain x-rays are normal. “Red flags” for these conditions include the following:

1. age > 70 years, or < 20 yrs
2. systemically ill patients
3. temp > 100°F (or > 38° C)
4. history of malignancy
5. recent infection
6. patients with neurologic deficits suggesting possible cauda equina syndrome (saddle anesthesia, urinary incontinence or retention, LE weakness, *see page 446*)
7. heavy alcohol or IV drug abusers
8. diabetics
9. immunosuppressed patients (including prolonged treatment with corticosteroids)
10. recent urinary tract or spinal surgery
11. *recent* trauma: any age with significant trauma, or > 50 yrs old with mild trauma
12. unrelenting pain at rest
13. persistent pain for more than ≈ 4 weeks
14. unexplained weight loss

When spine x-rays are indicated, AP and lateral views are usually adequate[32]. Obliques and coned-down L5-S1 views more than double the radiation exposure, and add information in only 4-8% of cases[33], and can be

obtained in specific instances where warranted (e.g. to diagnose spondylolysis when spondylolisthesis is found on the lateral film).

MRI

Unless contraindicated, MRI has supplanted CT and myelography for diagnosing most cases of disc herniation and spinal stenosis. Specificity and sensitivity for HLD are on the same order as CT/myelography, which is better than myelography alone[1, 34, 35].

Advantages:

1. provides information in sagittal plane (can easily evaluate cauda equina)
2. provides information regarding tissue outside of the spinal canal (e.g. extreme lateral disc herniation (*see page 453*), tumors…)
3. non-invasive and does not involve ionizing radiation

Disadvantages:

1. patients in severe pain or with claustrophobia may have difficulty holding still
2. dose not visualize bone well
3. poor for studying blood early (e.g. spinal epidural hematoma)
4. expensive (note: may be more cost effective than myelography if post-myelogram overnight hospitalization is avoided, and especially if a rare complication from myelography occurs)
5. interpretation with scoliosis is more difficult, may be partially compensated by contouring plane through which axial cuts are taken. Myelogram/CT may be superior
6. a number of contraindications: see *Contraindications to MRI*, page 130

Findings:

In addition to demonstrating herniated lumbar disc **(HLD)** outside of the disc interspace compressing nerve root or thecal sac, MRI can demonstrate signal changes within the interspace suggestive of <u>disc degeneration</u>[36] (loss of signal intensity on T2WI, loss of disc space height) and is useful in diagnosing infections and tumors.

Lumbosacral CT

Not considered state of the art. If technically adequate images can be obtained (e.g. good quality scanner, images not obscured by artifact from patient movement or obesity), CT can demonstrate most spine pathology. For HLD,

sensitivity is 80-95%, and specificity is 68-88%[37, 38]. However, even some large disc herniations will be missed with plain CT. CT studies for HLD tend to be less satisfactory in the elderly. More utility with fractures.

Disc material has density (Hounsfield units) ≈ twice that of the thecal sac. Associated findings with herniated disc include:

1. loss of epidural fat (normally seen as low density in the anterolateral canal)
2. loss of normal “convexity” of thecal sac (indentation by herniated disc)

Advantages:

1. images soft tissue to a degree that may be adequate
2. excellent bony detail
3. non-invasive
4. outpatient evaluation
5. evaluates for extreme lateral disc herniation to some degree
6. evaluates paraspinal soft tissue (e.g. to rule out tumor, paraspinal abscess…)
7. advantages over MRI: faster scanning (significant in patients who have difficulty laying still for long time), less expensive, less claustrophobic, fewer contraindications (see *Contraindications to MRI*, page 130)

Disadvantages:

1. does not evaluate sagittal plane (may be partially ameliorated by eliminating skip regions and then utilizing computerized sagittal reconstructions)
2. evaluates only those levels that are scanned:
   A. higher cuts must be taken through the conus medullaris to avoid missing occasional pathology there
   B. performing cuts only through the disc spaces (a common practice) may miss pathology between the disc spaces
3. sensitivity is significantly lower than MRI or myelogram/CT

Myelography

With water soluble contrast, sensitivity (62-100%) and specificity (83-94%)[39-42] are similar to CT for detection of HLD. When combined with post-myelographic CT scan (myelogram/CT), the sensitivity and especially specificity increase[43]. A herniated disk in the large space between thecal sac and posterior border of vertebral bodies at L5-S1 (**insensitive space**) may not be seen on

myelography (CT or MRI are usually better at detecting this).

Advantages:

1. provides information in sagittal plane (unlike plain CT)
2. evaluates cauda equina (unlike routine CT)
3. provides "functional" information about degree of stenosis (a high-degree block will allow flow of dye only after certain position changes)

Disadvantages:

1. occasionally requires overnight hospitalization
2. may miss pathology outside of the dura (including far laterally herniated disc), sensitivity is improved with post-myelographic CT
3. invasive
   A. drugs e.g. warfarin must be stopped, and sometimes converted to heparin
   B. with occasional side effects (post LP H/A, N/V, rare seizures)
4. iodine allergic patients
   A. requires iodine allergy prep
   B. may still be risky (especially in severely iodine allergic patients)

Findings:

HLD produces extradural filling defect at the level of the intervertebral disc. Massive disc herniation or severe lumbar stenosis may produce a total or near total block. In some cases of HLD, the finding may be very subtle and may consist of a cut-off of the filling (with contrast) of the nerve root sleeve (compared to normal nerve(s) on contralateral side or at other levels). Another subtle finding may be a "dual shadow" on lateral view.

Bone scan

See *page 432*

Discography

Injection of water-soluble contrast agent directly into the nucleus pulposus of the intervertebral disc being studied. Results of the test depend on volume of dye accepted into the disc, the pressure needed to inject the dye, the configuration of the dye (including leakage from the confines of the disc space) on radiographic imaging (plain x-rays produce the so-called "discogram", CT scan may also be utilized), and reproduction of the patient's pain on injection. Some of the basis for performing a discogram is to identify levels that may produce "discogenic

pain" or "painful disc syndrome", a controversial point (see *PRACTICE GUIDELINE 18-1*, page 434).

Critique:

Invasive. Interpretation is equivocal, and complications may occur (disc space infection, disc herniation, and significant radiation exposure with CT-discography). May be abnormal in asymptomatic patients[28, 29] (as any of the above tests may be) although the false positive rate may not be quite this high[44]. See *PRACTICE GUIDELINE 18-1*, page 434 for recommendations.

PSYCHOSOCIAL FACTORS

Although some patients with chronic LPB (> 3 months duration) may have started off with a diagnosable condition, psychological and socioeconomic factors (such as depression, secondary gain…) may come to play a significant role in perpetuating or amplifying pain. Psychological factors, especially elevated hysteria or hypochondriasis scales on the Minnesota Multiphasic Personality Inventory **(MMPI)** were found to be a better predictor of outcome than findings on radiographic imaging in one study[15]. A screening scale of 5 factors has been proposed[45] (positive findings in any 3 suggests psychological distress):

1. pain on simulated axial loading: press on top of head
2. inconsistent performance: e.g. difficulty tolerating straight leg raising **(SLR)** while supine, but no difficulty when sitting
3. overreaction during the physical exam
4. inappropriate tenderness that is superficial or widespread } these two items may not be reliable, the others are potentially reliable[46]
5. motor or sensory abnormalities not corresponding to anatomic confines } these two items may not be reliable, the others are potentially reliable[46]

However, the usefulness of this information is limited, and no effective interventions have been identified to address these factors. Therefore the AHCPR panel was unable to recommend specific assessment tools or interventions[1].

TREATMENT

An initial period of nonsurgical management (see *"Conservative" treatment* below) is indicated except in the following circumstances where urgent surgery is indicated: symptoms of a cauda equina syndrome (urinary retention, saddle

anesthesia…, see *Cauda equina syndrome*, page 446), progressive neurologic deficit, or profound motor weakness. A relative indication for proceeding to surgery without conservative management is severe pain that cannot be controlled with adequate pain medication (rare).

If specific diagnoses such as herniated intervertebral lumbar disc or symptomatic lumbar stenosis are made, surgical treatment for these conditions may be considered if the patient fails to improve satisfactorily. In cases where no specific diagnosis can be made, management consists of conservative treatment and following the patient to rule out the possible development of symptoms suggestive of a more serious diagnosis that may not have initially been evident.

"Conservative" treatment

This term has regrettably come to be used for non-surgical management. With slight modification, similar approaches can be used for mechanical low back pain, as well as for acute radiculopathy from disc herniation.

PRACTICE GUIDELINE 18-2 INJECTION THERAPY FOR LOW-BACK PAIN

Therapeutic recommendations

Level III[47]: lumbar epidural injections or trigger point injections are not recommended for long-term relief of chronic LBP. These techniques or facet injections may be used to provide temporary relief in select patients

Diagnostic recommendations

Level III[47]: **lumbar facet injections**

- may predict the response to radiofrequency facet ablation
- ✖ not recommended as a diagnostic tool to predict the response to lumbar fusion

Recommendations (based on AHCPR findings[1] in the absence of "red flags"[A]):

A. some key literature citations are given here, primarily those from the better studies that support the Agency for Health Care Policy and Research **(AHCPR)** panel recommendations. However, refer to Bigos et al.[1] for full analysis and list of references

1. activity modifications: no studies were found that met the panels review criteria for adequate evidence. However, the following information was felt to be useful:
   A. bed rest: for 2-3 days maximum
      1. the theoretical objective is to reduce symptoms by reducing pressure on the nerve roots and/or intradiscal pressures which is lowest in the supine semi-Fowler position[48], and also to reduce movements which are experienced as painful by the patient
      2. deactivation from prolonged bed rest (> 4 days) appears to be worse for patients (producing weakness, stiffness, and increased pain) than a gradual return to normal activities[49]
      3. recommendations: the majority of patients with low back problems will not require bed rest. Bed rest for 2-4 days may be an option for those with severe initial *radicular* symptoms, however, this may be no better than watchful waiting[50] and may be harmful[51]
   B. activity modification
      1. the goal is to achieve a tolerable level of discomfort while continuing sufficient physical activity to minimize disruption of daily activities
      2. risk factors: although there is not agreement on their exact role, the following were identified as having an increased incidence of low back problems. Jobs requiring heavy or repetitive lifting, total body vibration (from vehicles or industrial machinery), asymmetric postures, or postures sustained for long periods (including prolonged sitting)
      3. recommendations: temporarily limit heavy lifting, prolonged sitting, and bending or twisting of the back. Establish activity goals to help focus attention on expected return to full functional status
   C. exercise (may be part of a physical therapy program):
      1. during the 1st month of symptoms, low-stress aerobic exercise can minimize debility due to inactivity. In the first 2 weeks, utilize exercises that minimally stress the back: walking, bicycling, or swimming
      2. conditioning exercises for trunk muscles (especially back extensors, and possibly abdominal muscles) are helpful if symptoms persist (during the first 2 weeks, these exercises may aggravate symptoms)
      3. there is no evidence to support stretching of back muscles, or to

recommend back-specific exercise machines over traditional exercise

4. recommended exercise quotas that are gradually escalated results in better outcome than having patients simply stop when pain occurs[52]

2. analgesics:
   A. for the initial short-term period, acetaminophen **(APAP)** or NSAIDs (*see* *page 44*) may be used. In one study 53 of acute LBP, NSAIDs did not add any benefit to APAP + standard education (*see below*)
   B. stronger analgesics (mostly opioids, *see* *page 46*) may be required for severe pain, usually severe radicular pain. For non-specific back pain, there was no earlier return to full activity than with NSAIDs or APAP1. Opioids should not be used > 2-3 weeks, at which time NSAIDs should be instituted
3. muscle relaxants (*see* *page 50*)
   A. muscle spasms have not been proven to cause pain, and the most commonly used muscle relaxants have no peripheral effect on muscle spasm
   B. probably more effective than placebo, but have not been shown to be more effective than NSAIDs
   C. potential for side effects: drowsiness (in up to 30%). Most manufacturers recommend use for < 2-3 weeks. Agents such as chlorzoxazone (Parafon Forte® and others) may be associated with risk of serious and potentially fatal hepatotoxicity[54]
4. education: (may be provided as part of a physical therapy program)
   A. explanation of the condition to the patient[55] in understandable terms, and positive reassurance that the condition will almost certainly subside[56] have been shown to be more effective than many other forms of treatment
   B. proper posture, sleeping positions, lifting techniques… should be conveyed to the patient. Formal "back school" seems to be marginally effective[57]
5. spinal manipulation therapy **(SMT)**: defined as manual therapy in which loads are applied to the spine using long or short lever methods with the selected joint being taken to its end range of voluntary motion, followed by application of an impulse loading (may be part of a physical therapy program)

A. may be helpful for patients with acute low back problems without radiculopathy when used in the first month of symptoms (efficacy after 1 month is unproven) for a period not to exceed 1 month. One study[53] found no added benefit to APA + standard education
B. insufficient evidence to recommend SMT in the presence of radiculopathy
C. SMT should not be used in the face of severe or progressive neurologic deficit until serious conditions have been ruled out
D. ✖ reports of arterial dissection (especially vertebral artery - *see page 985*) and CVA, myelopathy & subdural hematoma with <u>cervical</u> SMT and cauda equina syndrome with lumbar SMT[58-60] and the uncertainty of benefits have led to the questioning of the use of SMT[58] (especially cervical)

6. epidural injections:
A. epidural steroid injections **(ESI)**: there is no evidence that this is effective in treating acute radiculopathy[61]. Prospective studies yield varied results[62]. Some improvement at 3 & 6 weeks may occur (but no functional benefit, and no change in the need for surgery), with no benefit at 3 months[63]. The response in chronic back pain is poor in comparison to acute pain. ESI may be an option for <u>short-term</u> relief of *radicular* pain when control on oral medications is inadequate or for patients who are not surgical candidates
B. there is no evidence to support the use of epidural injections of steroids, local anesthetics and/or opioids for LBP without radiculopathy
C. efficacy with conditions such as lumbar spinal stenosis are conflicting 62

✖ <u>Not</u> recommended by the AHCPR panel[1] for treatment of acute low back problems in the absence of “red flags” (see *Table 18-6*, page 432):

1. medications
A. oral steroids: no difference was found at one week and 1 year after randomization to receive 1 week therapy with oral dexamethasone or placebo[64]
B. colchicine: conflicting evidence shows either some[65] or no[66] therapeutic benefit. Side effects of N/V and diarrhea[1]
C. antidepressant medications: most studies of these medications were

for *chronic* back pain. Some methodologically flawed studies failed to show benefits when compared to placebo for chronic (not acute) LBP[67]

2. physical treatments
   A. TENS (transcutaneous electrical nerve stimulation): not statistically significantly better than placebo, and added no benefit to exercise alone[68]
   B. traction (including pelvic traction): not demonstrated to be effective[69]
   C. physical agents and modalities: including heat (including diathermy), ice, ultrasound. Benefit is insufficiently proven, however, self-administered home programs for application of heat or cold may be considered. Ultrasound and diathermy should not be used in pregnancy
   D. lumbar corsets and support belts: not proven beneficial for acute back problems. Prophylactic use has been advocated, but this is controversial[70]
   E. biofeedback: has not been studied for acute back problems. Primarily advocated for chronic LBP, where effectiveness is controversial[71]
3. injection therapy
   A. trigger point and ligamentous injections: the theory that trigger points cause or perpetuate LBP is controversial and disputed by many experts. Injections of local anesthetic are of equivocal efficacy
   B. (zygapophyseal) facet joint injections: theoretical basis is that there exists a "**facet syndrome**" producing LBP which is aggravated by spine extension, with no nerve root tension signs (*see page 443*). No studies have adequately investigated injections for pain < 3 months duration. For chronic LBP, neither the agent nor the location (intrafacet or pericapsular) made a significant difference in outcomes[72, 73]
   C. epidural injections in the absence of radiculopathy: *see above*
   D. acupuncture: no studies were found that evaluated the use in acute back problems. All randomized clinical trials found were for patients with *chronic* LBP, and even the best studies were felt to be mediocre and contradictory. Meta-analysis found acupuncture was more effective in relieving *chronic* LBP than sham or no treatment[74], but there was no comparison to other therapies

Surgical treatment

Indications for surgery for herniated lumbar disc:

See *page 445*.

Indications for fusion for chronic LBP without stenosis or spondylolisthesis: Very controversial. Guidelines are shown in *PRACTICE GUIDELINE 18-3*.

PRACTICE GUIDELINE 18-3 LUMBAR FUSION FOR LBP WITHOUT STENOSIS OR SPONDYLOLISTHESIS

Level I[75]: lumbar fusion is recommended for carefully selected patients* with disabling LBP due to one- or two-level degenerative disease without stenosis or spondylolisthesis

Level III[75, 77]: an intensive course of PT and cognitive therapy is recommended as a option for patients with LBP in whom conventional medical management has failed

* in the primary quoted study 76 patients had chronic LBP for ≥ 2 years and had radiologic evidence of disc degeneration at L4-L5, L5-S1, or both, and had failed best medical management

PRACTICE GUIDELINE 18-4 CHOICE OF FUSION TECHNIQUE

Level II[78]: for ALIF or ALIF + instrumentation, the addition of a posterolateral fusion is not recommended*

Level III[78]:

- either a posterolateral fusion or an interbody fusion (PLIF, TLIF or ALIF) are options for patients with LBP due to DDD at 1 or 2 levels
- an interbody graft is an option to improve fusion rates and functional outcome†
- ✖ the use of multiple approaches (anterior + posterior) is not recommended as a routine option for LBP without deformity

* the demonstrated benefit does not outweigh the additional time and blood loss involved

† caution: the improvement in fusion rate and outcome is marginal, and interbody fusion is associated with an increased complication rate, especially with combined approaches (e.g. 360° fusion)

TYPE OF SURGICAL TREATMENT

The type of surgical procedure chosen is tailored to the specific condition identified. Examples are shown in *Table 18-7*. Discussion of some options is also provided below.

Lumbar spinal fusion

Although there is no consensus on the indications[79], lumbar spinal fusion **(LSF)** is accepted treatment for fracture/dislocation or instability resulting from tumor or infection.

For degenerative spine disease, practice parameters have been developed and are included herein. Pain associated with Modic type 1 changes (*see page 430*) may respond to stabilization procedures, the other types do not exhibit this association.

Table 18-7 Surgical options for low back problems

Condition	Surgical treatment options
"routine" HLD	• standard discectomy and microdiscectomy are of similar efficacy • intradiscal procedures: nucleotome, laser disc decompression. Not recommended (*see page 447*) • chymopapain: acceptable, but less efficacious than above. Significant risk of anaphylaxis (*see page 447*). Use has been largely abandoned
foraminal or far lateral HLD	• partial or total facetectomy (*see page 454*) • extracanal approach (*see page 454*) • endoscopic techniques
lumbar spinal stenosis	• simple decompressive laminectomy • laminectomy plus fusion: may be indicated for patients with degenerative spondylolisthesis, stenosis and radiculopathy

PRACTICE GUIDELINE 18-5 LUMBAR FUSION FOR DISC HERNIATION

Level III[80]:

- lumbar fusion is <u>not</u> routinely recommended following disc excision in patients with HLD or recurrent HLD causing radiculopathy
- lumbar fusion is a potential adjunct to disc excision in cases of a HLD or recurrent HLD:
  - with evidence of preoperative lumbar spinal deformity or instability
  - in patients with chronic axial LBP associated with radiculopathy

Instrumentation as an adjunct to fusion

PRACTICE GUIDELINE 18-6 PEDICLE SCREW FIXATION

Level III[81]: pedicle screw fixation is recommended as a treatment option for patients with LBP treated with posterolateral fusion who are at high risk for fusion failure*

- -

** routine use of pedicle screws is discouraged because of conflicting evidence of benefit, together with considerable evidence of increased cost and complications*

The use of instrumentation increases the fusion rate[82]. Hardware used in the absence of fusion will eventually fatigue, especially in the region of the lumbar lordosis. Therefore, instrumentation must be viewed as a temporary internal stabilizing measure while awaiting the fusion process to complete.

CHRONIC LOW BACK PAIN

Rarely can an anatomic diagnosis be made in patients with chronic LBP ≥ 3 months[83]. Also, see *Psychosocial factors*, page 436. Patients with chronic pain syndromes **(CPS)** refer to their problems with affective or emotional terms with a higher frequency than those with acute pain[84]. The amount of time that a patient has been out of work due to low back problems is related to the chances of the patient getting back to work as shown in *Table 18-8*.

Table 18-8 Chances of patients going back to work

Time out of work	Chances of getting back to work
< 6 mos	50%
1 yr	20%
2 yrs	< 5%

18.1.1. Post-op clinic visits - lumbar fusion

Patients are seen in the clinic at intervals depending on the preference of the surgeon. A typical follow-up schedule with studies routinely performed is shown in *Table 18-9*. For specific problems, additional investigations are usually needed.

Post-op x-rays: Items to check on post op x-rays include:

1. alignment
2. position of grafts if used (e.g. inter-body grafts)
3. integrity of hardware (look for screw or rod breakage, screw pullout, rod disconnection)
4. lucencies around screws which may indicate motion and implies non-union
5. any evidence of fusion (may be difficult, e.g. with synthetic interbody fusions)
6. flexion/extension films: look for motion across fused segments

(sometimes absence of motion is the only evidence of fusion on plain x-rays) and the development of abnormal motion at adjacent segments

Table 18-9 Sample post-op lumbar fusion clinic visit schedule

Time post-op	Agenda
7-10 d	wound check, D/C sutures/staples if used
6 wks	AP & lateral LS-spine x-ray in brace
10-12 wks	• AP & lateral LS-spine x-rays with flexion/extionsion views out of brace • if x-rays look good and patient is doing well, begin weaning brace
6 months	• AP & lateral LS-spine x-rays with flexion/extension views • some surgeons release patients at this time if they are doing well
1 year (optional)	• AP & lateral LS-spine x-rays with flexion/extension views • release patient if they are doing well

18.2. Sagittal balance

The normal curvature of the spine in the sagittal plane (cervical lordosis, thoracic kyphosis and lumbar lordosis) permits standing posture with the minimum of muscle activity and soft tissue deformity. Abnormalities in any component of this sagittal balance **(SB)** result in compensatory changes in other segments.

Hardacker et al[85] proposes the following (angles measured using Cobb's technique (*see page 430*)):

1. cervical lordosis: normally 40° ± 9.7°
2. the occipital cervical junction is actually in kyphosis
3. the majority of lordosis occurs between C1-C2
4. the lower cervical spine (C4-C7) is relatively flat with an average lordosis of 6°
5. thoracic kyphosis: normally 20-50°. Increases with age (especially significant in age > 40 yrs) and the rate of increase is higher in females[86] (*see Table 18-10* for normal values)
6. lumbar lordosis: normally 31-79°

To assess sagittal balance, on a standing lateral full-spine xray: a **plumb line** is drawn straight down from the center of the C7 VB (*see Figure 18-2*). There are various definitions for where the line should cross for normal sagittal balance, including:

1. the plumb line should pass within the L5-S1 disc space or within 2 cm of the sacral promontory and through or behind the axis of the hip joint
2. the mean sagittal vertical axis fell 3.2 ± 3.2 cm behind the front of the sacrum in asymptomatic patients > 40 years old[87]

A plumb line can also be drawn from the center of C2 down, and this line should pass through the C7 VB and then on to the same lumbosacral targets as above.

Patients with compensated sagittal balance can temporarily correct for an abnormal plumb line using back muscles and pelvic tilt which leads to pain and fatigue.

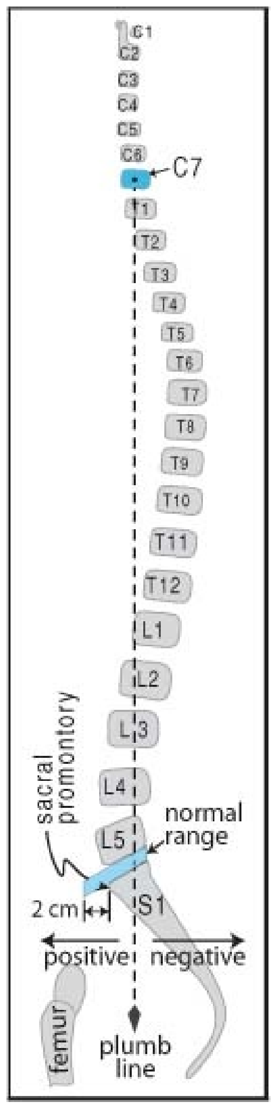

Figure 18-2 Sagittal balance plumb line Lateral spine schematic

Etiologies of loss of sagittal balance

1. congenital: Scheuermann's thoracic hyperkyphosis
2. aging: cervical lordosis and thoracic kyphosis increase, lumbar lordosis decreases
3. traumatic
4. iatrogenic: post-op flat-back syndrome
5. pathologic: osteoporosis
6. neuromuscular disorders

Clinical features:

1. pain
2. deformity
3. difficulty ambulating

Table 18-10 Normal values for thoracic kyphosis[86]*

Age (yrs)	Kyphosis (± SD)	
	Males	Females
< 10	20° (± 7.85)	24° (± 6.67)
10-19	25° (± 8.16)	26° (± 7.43)
40-49	30° (± 6.93)	33° (± 6.72)
50-59	33° (± 6.46)	41° (± 9.88)
70-79	41° (± 7.57)	42° (± 9.00)

* measured using a modified Cobb technique in asymptomatic patients

Flat back syndrome: AKA lumbar degenerative kyphosis. More common in Asia than Western countries. May also occur following lumbar fusion. Management: controversial. Restoring lost sagittal balance may cause improvement of symptoms[88].

Surgical management: for flexible deformity, the spine may be fused after sagittal balance is restored either manually or posturally. For fixed deformities, options to increase lumbar lordosis:

1. Smith-Peterson (facet) osteotomy: shortens posterior elements and lengthens anterior elements. Anterior elements may be lengthened using interbody grafts placed from an anterior approach
2. pedicle subtraction osteotomy: decreases pedicle and posterior VB. Does not produce an anterior defect

18.3. Intervertebral disc herniation

18.3.1. Lumbar disc herniation

Key concepts:

- typical disc herniation → radiculopathy in the nerve exiting at the level below
- massive disc herniations can → cauda equina syndrome (a medical emergency). Typical symptoms: saddle anesthesia, urinary retention, LE weakness (*page 446*)
- most patients do as well with conservative treatment as with surgery, ∴ initial conservative treatment should be considered for the vast majority
- surgery indications: cauda equina syndrome, progressive symptoms or neurologic deficits despite conservative treatment, or severe *radicular* pain $> \approx 6$ weeks

PATHOPHYSIOLOGY

Intervertebral discs may undergo degenerative changes (see *Table 18-1*, page 429 for description) which increases the risk of herniation (see same table for definition).

Variants:

1. intravertebral disc herniation (Schmorl's node): *see page 455*
2. intradural disc herniation: *see page 455*
3. **limbus fracture**: traumatic separation of a segment of bone from the edge of the vertebral ring apophysis at the site of anular attachment. May accompany HLD

CLINICAL ASPECTS

The posterior longitudinal ligament is strongest in the midline, and the posterolateral annulus may bear a disproportionate portion of the load. This may explain why most herniated lumbar discs **(HLD)** occur posteriorly, slightly off to one side, characteristically compressing the nerve root en passage → severe radicular pain.

Characteristic findings on the history often include:

1. symptoms may start off with back pain, which after days or weeks gradually or sometimes suddenly yields to radicular pain often with reduction of the back pain
2. precipitating factors: various factors are often blamed, but are rarely identified[89] with certainty
3. pain relief upon flexing the knee and thigh
4. patients generally avoid excessive movements, however, remaining in any one position (sitting, standing, or lying) too long may also exacerbate the pain, sometimes necessitating position changes at intervals that range from every few minutes to 10-20 minutes. This is distinct from constant writhing in pain e.g. with ureteral obstruction
5. "**cough effect**": ↑ pain with coughing, sneezing, or straining at the stool. Occurred in 87% of patients with HLD in one series[90]
6. **bladder symptoms**: the incidence of voiding dysfunction is 1-18%[91 (p 966)]. Most common: difficulty voiding, straining, or urinary retention. Reduced bladder sensation may be the earliest finding. Later it is not unusual to see "irritative" symptoms including urinary urgency, frequency (including nocturia), increased post-void residual. Less common: enuresis, and dribbling incontinence[92] (NB: frank urinary retention may indicate cauda equina syndrome, *see page 446*). Occasionally a HLD may present only with bladder symptoms which may improve after surgery[93]. Discectomy may improve bladder function, but this cannot be assured

PHYSICAL FINDINGS IN RADICULOPATHY

Back pain per se is usually a minor component (only 1% of patients with acute low back pain have sciatica[4]), and when it is the only presenting symptom, other causes should be sought (see *Low back pain*, page 1192). Sciatica has such a high sensitivity for disc herniation, that the likelihood of a clinically significant disc herniation[94] in the absence of sciatica is ≈ 1 in 1000. Exceptions include a central disc herniation which may cause symptoms of lumbar stenosis (i.e. neurogenic claudication) or a cauda equina syndrome.

Nerve root impingement gives rise to a set of signs and symptoms present to variable degrees. Characteristic syndromes are described for the most common nerve roots involved (see *Nerve root syndromes* below).

In a series of patients referred to neurosurgical outpatient clinics for radiating leg pain, 28% had motor loss (yet only 12% listed motor weakness as a presenting complaint), 45% had sensory disturbance, and 51% had reflex

changes[95].

Findings suggestive of nerve root impingement include the following. *Table 18-11* shows the sensitivity and specificity of some findings on the exam among patients with sciatica.

1. signs/symptoms of radiculopathy (see *Table 18-13*, page 445)
   A. pain radiating down LE
   B. motor weakness
   C. dermatomal sensory changes
   D. reflex changes: mental factors may influence symmetry[96]
2. positive nerve root tension sign(s): including Lasègue's sign (*see below*)
3. tenderness over the sciatic notch

Table 18-11 Sensitivity and specificity of physical findings for HLD in patients with sciatica[1]

Test	Comment	Sensitivity	Specificity
ipsilateral SLR	positive result: pain at < 60° elevation	0.80	0.40
crossed SLR	reproduction of contralateral pain	0.25	0.90
↓ ankle jerk	HLD usually at L5-S1 (total absence increases specificity)	0.50	0.60
sensory loss	area of loss is poor in localizing level of HLD	0.50	0.50
↓ patellar reflex	suggests upper HLD	0.50	NA
WEAKNESS			
knee extension (quadriceps)	HLD usually at L3-4	< 0.01	0.99
ankle dorsiflexion (anterior tibialis)	HLD usually at L4-5	0.35	0.70
ankle plantarflexion (gastrocs)	HLD usually at L5-S1	0.06	0.95
great toe extension (EHL)	HLD at L5-S1 in 60%, at L4-5 in 30%	0.50	0.70

Nerve root tension signs

Includes[97]:

1. **Lasègue's sign**: AKA straight leg raising **(SLR)** test. Helps differentiate sciatica from pain due to hip pathology. Test: with patient supine, raise afflicted limb by the ankle until pain is elicited[98] (should occur at **< 60°**,

tension in nerve increases little above this angle). A positive test consists of leg pain or paresthesias in the distribution of pain (back pain alone does not qualify). The patient may also extend the hip (by lifting it off table) to reduce the angle. Although not part of Lasègue's sign, ankle dorsiflexion with SLR usually augments pain due to nerve root compression. SLR primarily tenses L5 and S1, L4 less so, and more proximal roots very little. Nerve-root compression produces a positive Lasègue's sign in ≈ 83% of cases[90] (more likely to be positive in patients < 30 yrs age with HLD[99]). May be positive in lumbosacral plexopathy (*see page 795*). Note: flexing both thighs with the knees extended ("long-sitting" or sitting knee extension) may be tolerated further than flexing the single symptomatic side alone

2. **Cram test**: with patient supine, raise the symptomatic leg with the knee slightly flexed. Then, extend the knee. Results similar to SLR
3. **crossed straight leg-raising** test AKA **Fajersztajn's sign**: SLR on the painless leg causes contralateral limb pain (a greater degree of elevation is usually required than the painful side). More specific but less sensitive than SLR (97% of patients undergoing surgery with this sign have confirmed HLD[100]). May correlate with a more central disc herniation
4. **femoral stretch test**[101], AKA **reverse straight leg raising**: patient prone, examiner's palm at popliteal fossa, knee is maximally dorsiflexed. Often positive with L2, L3, or L4 nerve root compression (e.g. in upper lumbar disc herniation), or with extreme lateral lumbar disc herniation (may also be positive in diabetic femoral neuropathy or psoas hematoma); in these situations SLR (Lasègue's sign) is frequently negative (since L5 & S1 not involved)
5. "**bowstring sign**": once pain occurs with SLR, lower the foot to the bed by flexing knee, keeping the hip flexed. Sciatic pain ceases with this maneuver, but hip pain persists
6. **sitting knee extension** test: with patient seated and both hips and knees flexed 90°, slowly extend one knee. Stretches nerve roots as much as a moderate degree of SLR

Other signs useful in evaluation for lumbar radiculopathy

1. **FABER**: an acronym for Flexion ABduction External-Rotation, AKA FABERE test (the trailing "e" is for extension), AKA Patrick's-test. A test

of hip motion. Method: the hip and knee are flexed and the lateral malleolus is placed on the contralateral knee. The ipsilateral knee is gently displaced downward towards the exam table. This stresses the hip joint and does not usually exacerbate true nerve-root compression. Often markedly positive in the presence of hip joint disease (e.g. trochanteric bursitis, *see page 478*), sacroiliitis or mechanical low-back pain

2. **Trendelenburg sign**: examiner observes pelvis from behind while patient raises one leg while standing. Normally the pelvis remains horizontal. A positive sign occurs when the pelvis tilts down toward the side of the lifted leg indicating weakness of the contralateral thigh adductors (primarily L5 innervated)
3. **crossed adductors**: in eliciting patellar reflex (knee jerk **(KJ)**), the contralateral thigh adductors contract. In the presence of a hyperactive ipsilateral KJ it may indicate an upper motor neuron lesion, in the presence of a hypoactive ipsilateral KJ it may be a form of pathological spread, indicating nerve root irritability
4. **Hoover sign** 102: to distinguish unilateral functional weakness of iliopsoas from organic weakness using synergistic contraction of the contralateral gluteus medius. The supine patient is asked to lift one leg off the bed against resistance from the examiner's hand. The examiner simultaneously places the palm of his/her other hand under the heel of the unlifted leg and gently lifts. Test 1: when the patient lifts the normal leg, if the paretic leg pushes down with more force than was exhibited on manual testing of the limb beforehand, the weakness is judged functional, if the force is equally weak the weakness is judged organic. Test 1 cannot be used if the hip extensor was normal beforehand. Test 2: (the better known test) the patient is asked to lift the weak leg. If the heel on the normal side lifts passively by the examiner, it suggests the weakness is functional (i.e. the patient is not trying). Not totally reliable[103, 104]
5. **abductor sign**: an alternative to the Hoover test, to differentiate functional from organic weakness in the thigh abductors using synergistic contraction of the contralateral thigh abductors[104]. With the patient supine, the examiner places a hand on the lateral aspect of both legs. The patient is asked to abduct legs. The patient is asked to abduct one leg, and then the other while the examiner applies resistance with his/her hand. The examiner mentally notes the response of the *non-abducting* LE. The results are as noted in *Table 18-12*

Table 18-12 Abductor sign

Abducting LE	Contralateral (nonabducting) LE	
	Organic weakness	Functional weakness
weak LE	maintains position	hyperadducts
normal LE	hyperadducts	maintains position

Nerve root syndromes

Due to the facts listed below, a herniated lumbar disc **(HLD)** usually spares the nerve root exiting at that interspace, and impinges on the nerve exiting from the neural foramen one level below (e.g. a L5-S1 HLD usually causes S1 radiculopathy). This gives rise to the characteristic lumbar nerve root syndromes shown in *Table 18-13*.

Important facts in lumbar disc disease:

1. in the lumbar region, the nerve root exits below and in close proximity to the pedicle of its like-numbered vertebra
2. the intervertebral disc space is located well below the pedicle
3. not all patients have 5 lumbar vertebrae (see *Localizing levels in spine surgery*, page 173)

Table 18-13 Lumbar disc syndromes

	— Level of herniated lumbar disc —		
	L3-4	**L4-5**	**L5-S1**
root usually compressed	L4	L5	S1
% of lumbar discs	3-10% (5% average)	40-45%	45-50%
reflex diminished	knee jerk* (Westphal's sign)	medial hamstring†	Achilles* (ankle jerk)
motor weakness	quadriceps femoris (knee extension)	tibialis anterior (foot drop) & EHL‡	gastrocnemius (plantarflexion), ± EHL‡
decreased sensation§	medial malleolus & medial foot	large toe web & dorsum of foot	lateral malleolus & lateral foot
pain distribution	anterior thigh	posterior LE	posterior LE, often to ankle

* **Jendrassik maneuver** may reinforce (*see page 786*)

† medial hamstring reflex is unreliable (not always pure L5), may also stimulate adductors when eliciting

‡ see WEAKNESS in *Table 18-11*, page 443 for breakdown

§ sensory impairment is most common in the distal extremes of the dermatome[105]

Radiographic evaluation

See *Radiographic evaluation* on page 433 under *Low back pain*.

NONSURGICAL TREATMENT

For nonsurgical treatment, see *"Conservative" treatment*, page 437.

SURGICAL TREATMENT

INDICATIONS

No predictive factors have been identified that can determine which patients are likely to improve on their own and which would be better served with surgery.

Surgical indications in patients with a radiographically identified herniated disc that correlates with findings on the history and physical exam:

1. failure of non-surgical management to control pain after 5-8 weeks: over 85% of patients with acute disc herniation will improve without surgical intervention in an average of 6 weeks[106] (70% within 4 weeks[107]). Most clinicians advocate waiting somewhere between 5-8 weeks from the onset of radiculopathy before considering surgery (assuming none of the items listed below applies)
2. **"EMERGENT SURGERY":** (i.e. before the 5-8 weeks have lapsed). Indications:
   A. cauda equina syndrome **(CES)**: (*see below*)
   B. progressive motor deficit (e.g. foot drop). NB: paresis of unknown duration is a doubtful indication for surgery[89, 108, 109] (no study has documented that there is less motor deficit in surgically treated patients with this finding[110]). However, the acute development or progression of motor weakness is considered an indication for rapid surgical decompression
   C. "urgent" surgery may be indicated for patients whose pain remains intolerable in spite of adequate narcotic pain medication
3. ± patients who do not want to invest the time in a trial of non-surgical treatment if it is possible that they will still require surgery at the end of the trial

Cauda equina syndrome

The clinical condition arising from dysfunction of multiple lumbar and sacral nerve roots within the lumbar spinal canal. Usually due to compression of the

cauda equina. See *Table 21-86*, page 744 for features to help differentiate CES from a conus lesion.

Possible **findings** in CES:

1. sphincter disturbance:
   A. urinary retention: the most consistent finding. Sensitivity ≈ 90% (at some point in time during course)[111, 112]. To evaluate acutely: have patient empty bladder and check post-void residual (by catheterization or with bladder ultrasound). In a patient without retention, only 1 in 1000 will have a CES. Cystometrogram (when done) shows a hypotonic bladder with decreased sensation and increased capacity
   B. urinary and/or fecal incontinence[113]: some patients with urinary retention will present with overflow incontinence
   C. anal sphincter tone: diminished in 60-80%
2. "**saddle anesthesia**": the most common sensory deficit. Distribution: region of the anus, lower genitals, perineum, over the buttocks, posterior-superior thighs. Sensitivity ≈ 75%. Once total perineal anesthesia develops, patients tend to have permanent bladder paralysis[114]
3. significant motor weakness: usually involves more than a single nerve root (if untreated, may progress to paraplegia)
4. low back pain and/or sciatica (sciatica is usually bilateral, but may be unilateral or entirely absent, prognosis may be worse when absent or bilateral[112])
5. bilateral absence of Achilles reflex has been noted[115]
6. sexual dysfunction (usually not detected until a later time)

Etiologies of CES includes:

1. compression of cauda equina
   A. massive herniated lumbar disc: *see below*
   B. tumor
      1. from compression: e.g. with metastatic disease to the spine with epidural extension
      2. **intravascular lymphomatosis (B-cell lymphoma)**: a circulating lymphoma without solid mass (*see page 674*). Often presents with CNS findings: dementia, enhancing meninges on MRI, lymphoma cells in CSF, and CES
   C. free fat graft following discectomy[116]
   D. trauma: fracture fragments compressing cauda equina

    E. spinal epidural hematoma
2. infection: may cause neurologic deficit from
    A. compression: typically from spinal epidural abscess complicating discitis or vertebral osteomyelitis
    B. a significant number of cases of CES from infection may be due to vascular compromise resulting from local septic thrombophlebitis. This may carry a worse prognosis as surgical decompression cannot correct this mechanism
3. neuropathy:
    A. ischemic
    B. inflammatory
4. ankylosing spondylitis: etiology is often obscure (*see page 502*)

CES from HLD: May be due to massive herniated disc, usually midline, most common at L4-5, often superimposed on a preexisting condition (spinal stenosis, tethered cord…)[113].

Prevalence of CES:
1. 0.0004 in all patients with LBP[94]
2. only ≈ 1-2% of HLD that come to surgery[94]

Time course: CES tends to develop either acutely, or (less typically) slowly (prognosis is worse in the acute onset group, especially for return of bladder function, which occurred in only ≈ 50%)[111]. 3 patterns[117]:
- Group I - sudden onset of CES symptoms with no previous low back symptoms
- Group II - previous history of recurrent backache and sciatica, the latest episode combined with CES
- Group III - presentation with backache & bilateral sciatica that later develop CES

Surgical issues: some advise a bilateral laminectomy[113] (but this is not mandatory). Occasionally, when it is difficult to remove a very tense midline disc, transdural removal may be helpful[115].

Timing of discectomy in CES: controversial, and the point of contention in numerous law suits. In spite of early reports emphasizing rapid decompression[115], other re-ports found no correlation between the time to surgery after presentation and the return of function[111, 112]. Some evidence supports the goal of performing surgery **within 48 hours** (although performing

surgery within 24 hours is desirable if possible, there is no statistically significant proof that delaying up to 48 hrs is detrimental)[118, 119].

Booking the case - lumbar discectomy

Also see defaults & disclaimers (*page v*).

1. position: prone
2. equipment: microscope (if used), minimally invasive retractors (if used)
3. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: through the back to go between the bones and remove the piece of disc that is pressing on the nerve(s)
   B. alternatives: nonsurgical management
   C. complications: (usual spine surgery complications - *see page v*) *plus* the disc can herniate again in the same place in ≈ 6% of cases, it is possible that a fragment of disc can be missed at the time of surgery, there might not be the amount of pain relief desired (back pain does not respond as well to surgery as nerve-root pain),

Surgical options for lumbar radiculopathy

Once it is decided to treat surgically, options include:

1. trans-canal approaches
   A. standard open lumbar laminectomy and discectomy: 65-85% reported no sciatica one year post-op compared to 36% for conservative treatment[120]. Long-term results (> 1 year) were similar. 10% of patients underwent further back surgery during the first year[120]
   B. "microdiscectomy"[121, 122]: similar to standard procedure, however smaller incision is utilized. Advantages may be cosmetic, shortened hospital stay, lower blood loss. May be more difficult to retrieve some fragments[123 (p 1319), 124]. Overall efficacy is similar to standard discectomy[125]
   C. sequestrectomy: removal of only the herniated portion of disc
2. intradiscal procedures (*see below*)
   A. chemonucleolysis: using chymopapain (*see below*)
   B. automated percutaneous lumbar discectomy: utilizes a nucleotome
   C. percutaneous endoscopic discectomy: *see below*
   D. intradiscal endothermal therapy (**IDET** or **IDTA**): *see below*

E. laser disc decompression

Chemonucleolysis

Acceptable treatment, but less efficacious than discectomy[1] ("open" or micro). **Chymopapain** (Chymodiactin®) is injected intradiscally. Proven more effective than placebo injection[126, 127]. Typical success rates: at 1 year 85% of patients undergoing discectomy had good or excellent results compared to 44%[128] to 63%[129] for chemonucleolysis **(CNL)**. Although sciatica improves in both groups, only the discectomy group had significant improvement in back pain[128]. In one study, at 6 months 56% of patients initially having CNL had undergone surgery for unrelieved symptoms[130].

Risks[131, 132]:

Risk of the significant complication of anaphylaxis (sometimes fatal) may be reduced by skin-tests for allergic sensitivity to the agent. Other complications reported include: discitis[133], neurologic injury, vascular injury, thrombophlebitis, PE, transverse myelitis[134] (very uncommon).

Intradiscal surgical procedures (ISP)

ISPs (*see below* for specific procedures) are among the most controversial procedures for lumbar spine surgery. The theoretical advantage is that epidural scarring is avoided, and that a smaller incision or even just a puncture site is used. This is also purported to reduce postoperative pain and hospital stay (often performed as an outpatient procedure). The conceptual problem with ISPs is that they are directed at removing disc material from the center of the disc space (which is not producing symptoms) and rely on the reduced intradiscal pressure to decompress the herniated portion of the disc from the nerve root. Only ≈ 10-15% of patients considered for surgical treatment of disc disease are candidates for an ISP. ISPs are usually done under local anesthetic in order to permit the patient to report nerve root pain to identify impingement on a nerve root by the surgical instrument or needle. Overall, ISPs are not recommended until controlled trials prove the efficacy[1].

Indications utilized by proponents of intradiscal procedures:

1. type of disc herniation: appropriate only for "contained" disc herniation (i.e. outer margin of anulus fibrosus intact)
2. appropriate level: best for L4-5 HLD. May also be used at L3-4. Difficult

but often workable (utilizing angled instruments or other techniques) at L5-S1 because of the angle required and interference by iliac crest

3. not recommended in presence of severe neurologic deficit[135]

Results:

"Success" rate (≈ pain free and return to work when appropriate) reported ranges from 37-75%[136-138].

Automated percutaneous lumbar discectomy: AKA nucleoplasty. Utilizes a nucleotome[139] to remove disc material from the center of the intervertebral disc space. Significantly less efficacious than chymopapain[138], with 1 year success rate of 37% (compared to 66% for CNL). Complications include cauda equina syndrome from improper nucleotome placement[140]. In another study, nucleoplasty (with or without IDET (*see below*)) for HLD showed only modest reduction in pain at 9 months[141].

Laser disc decompression: Insertion of a needle into the disc, and introduction of a laser fiberoptic cable through the needle to allow a laser to burn a hole in the center of the disc[142, 143] (with or without endoscopic visualization).

Percutaneous endoscopic lumbar discectomy (PELD): This term refers to an essentially intradiscal procedure indicated primarily for contained disc herniations, although some small "noncontained" fragments may be treatable[144]. No large randomized study has been done to compare the technique to the accepted standard, open discectomy (with or without microscope). In one report[145] of 326 patients with L4-5 HLD, only 8 (2.4%) met study criteria (no previous operation, failure of conservative treatment, imaging study proving disc protrusion followed by discography to R/O "disc perforation") for PELD. Of these 8, only 3 were reported as having a good result. This study is not adequate for evaluating the technique.

Intradiscal endothermal therapy (IDET): AKA intradiscal (electro)thermal anuloplasty **(IDTA)**. Efficacy: 23-60% at 1 year for treating "internal disc disruption"[146] (radial fissures in the nucleus pulposus extending into the anulus fibrosus) which is purported to account for 40% of patients with chronic low back pain of unknown etiology[147].

Adjunctive treatment in lumbar laminectomy

Epidural steroids following discectomy

In a single-blinded non-randomized study of the use of epidural steroids (methylprednisolone acetate (Depo-Medrol®), dose not specified) irrigation of the thecal sac and nerve root following discectomy prior to wound closure found no statistically significant evidence of benefit in terms of amount of post-op analgesic medication needed, duration of hospital stay, or time to return to work[148]. However, the combination of *systemic* steroids at the start of the case (Depo-Medrol® 160 mg IM and methylprednisolone sodium succinate (Solu-Medrol®) 250 mg IV) combined with infiltration of 30 ml of 0.25% bipuvicaine (Marcaine®) into the paraspinal muscles at incision and closure, may reduce hospital stay and post-op narcotic requirements[149].

Methods to reduce scar formation

Epidural free fat graft: The use of an autogenous free fat graft in the epidural space has been employed in an attempt to reduce post-op epidural scar formation. Opinion varies widely as to the effectiveness, some feel it is helpful, others feel it actually exacerbates scarring[150]. In some patients, no evidence of the graft will be found on reoperation years later. The fat graft can very rarely be a cause of nerve root compression[151] or cauda equina syndrome[116] within the first few days post-op, and there is a case report of compression 6 years following surgery[152].

Other measures: Other measures include the placement of barrier films or gels. There are numerous products available, none has been shown to have reproducible benefit.

Risks of lumbar laminectomy

Overall risk of mortality in large series[153, 154]: 6 per 10,000 (i.e. 0.06%), most often due to septicemia, MI, or PE. Complication rates are very difficult to determine accurately[120], but the following is included as a guideline.

Common complications

(consider discussing these as part of informed consent)

1. infection:
   A. superficial wound infection: 0.9-5%[155] (risk is increased with age, long term steroids, obesity, ? DM): most are caused by *S. aureus* (see

Laminectomy wound infection, page 348 for management)
   B. deep infection: < 1%(*see below* under *Uncommon complications*)
2. increased motor deficit: 1-8% (some transient)
3. unintended "incidental" durotomy[A]: (*see below*) incidence is 0.3-13% (risk increases to ≈ 18% in re-do operations)[156]. Possible sequelae include those listed in *Table 18-14*
   A. CSF fistula (external CSF leak): the risk of a CSF fistula requiring operative repair is ≈ 10 per 10,000153
   B. pseudomeningocele: 0.7-2%[156] (may appear similar radiographically to spinal epidural abscess **(SEA)**, but post-op SEA often enhances, is more irregular, and is associated with muscle edema)
4. recurrent herniated lumbar disc (same level either side): 4% (with 10 year followup)[157] (*see page 460*)

A. the term "unintended durotomy" has been recommended in preference to "dural tear" (*see below*)

Uncommon complications

1. direct injury to neural structures. For large disc herniations, consider a bilateral exposure to reduce risk
2. injury to structures anterior to the vertebral bodies **(VB)**: injured by breaching the anterior longitudinal ligament **(ALL)** through the disc space, e.g. with pituitary rongeur. The depth of disc space penetration with instruments should be kept **≤ 3 cm**, since 5% of lumbar discs had diameters as small as 3.3 cm[158]. Asymptomatic perforations of the ALL occur in up to 12% of discectomies. Breach of the ALL risks potential injuries to:
   A. great vessels[159]: risks include potentially fatal hemorrhage, and arteriovenous fistula which may present years later. Most such injuries occur with L4-5 discectomies. Only ≈ 50% bleed into the disc space intraoperatively, the rest bleed into the retroperitoneum. Emergent laparotomy is indicated, preferably by a surgeon with vascular surgical experience, if available. Mortality rate is 37-67%
      1. aorta: the aortic bifurcation is on the left side of the lower part of the L4 VB, and so the aorta may be injured above this level
      2. below L4, the common iliac arteries may be injured

        3. veins (more common than arterial injuries)
            a. vena cava at and above L4
            b. common iliac veins below L4
    B. ureters
    C. bowel: at L5-S1 the ileum is the most likely viscus to be injured
    D. sympathetic trunk
3. wrong site surgery: incidence in self-reporting survey was 4.5 occurrences per 10,000 lumbar spine operations[160]. Factors identified as potential contributors to the error: unusual patient anatomy, not performing localizing radiograph. 32% of responding neurosurgeons indicated that they removed disc material from the wrong level at some time in their career
4. rare infections:
    A. meningitis
    B. deep infection: < 1%. Including:
        1. discitis: 0.5% (*see* *page 383*),
        2. spinal epidural abscess **(SEA)**: 0.67% (*see* *page 376*)
5. cauda equina syndrome: may be caused by post-op spinal epidural hematoma (*see below*). Incidence was 0.21% in one series of 2842 lumbar discectomies[161] and 0.14% in a series of 12,000 spine operations[162]. Red flags: urinary retention, anesthesia that may be saddle or <u>bilateral LE</u>
6. postoperative visual loss **(POVL)**[163]:
    A. ischemic optic neuropathy[164]: the most common cause of POVL. Commonly bilateral. Usually associated with significant blood loss (**median: 2 L**), and/or prolonged operative time (**≥ 6 hrs**). All cases had anesthetic time > 5 hrs or blood loss > 1 L. Blood loss can cause hypotension (may cause release of endogenous vasoconstrictors in addition to reduced blood flow due to low hemodynamic pressure) and increased platelet aggregation. Is <u>not</u> due to direct pressure on the globe in most cases, and can occur at any age and even in otherwise healthy patients. Blindness can be extensive and is often permanent, although early aggressive treatment may result in some improvement
        1. posterior ischemic optic neuropathy **(PION)**[164]: may follow surgery (surgical PION). Risk factors as above, plus:
            a. surgery in the <u>prone</u> position (can cause peri-orbital edema, and rarely, direct pressure on the orbit)
            b. lack of tight glycemic control

c. use of Trendelenburg position
d. hemodilution or overuse of crystalloid vs. colloid (blood) fluid replacement
e. prolonged hypotension
f. cellular hypoxia
g. decreased renal perfusion
2. anterior ischemic optic neuropathy (AION): divided into arteritic (as with GCA) and nonarteritic (common with DM)
B. central retinal artery occlusion
C. cortical blindness
7. complications of positioning:
A. compression neuropathies: ulnar, peroneal nerves. Use padding over elbows and avoid pressure on posterior popliteal fossa
B. anterior tibial compartment syndrome: due to pressure on anterior compartment of leg (reported with Andrew's frame). An orthopedic emergency that may require emergent fasciotomy
C. pressure on the eye: corneal abrasions, damage to the anterior chamber
D. cervical spine injuries during positioning due to relaxed muscles under anesthesia
8. post op arachnoiditis: risk factors include epidural hematoma, patients who tend to develop hypertrophic scar, post op discitis, and intrathecal injection of Pantopaque®, anesthetic agents or steroids. Surgical treatment is disappointing. Intrathecal depo-medrol may provide short-term relief (in spite of the fact that steroids are a risk factor for the development of arachnoiditis). Also *see page 458*
9. thrombophlebitis and deep-vein thrombosis with risk of pulmonary embolism **(PE)**[153]: 0.1% (see *Thromboembolism in neurosurgery*, page 42)
10. complex regional pain syndrome AKA reflex sympathetic dystrophy **(RSD)**: reported in up to 1.2% of cases, usually after posterior decompression with fusion, often following reoperations[165] with onset 4 days to 20 weeks post-op. *See page 576* for a critique of RSD. Treatment includes some or all of: PT, sympathetic blocks, oral methylprednisolone, removal of hardware if any
11. very rare: Ogilvie's syndrome (pseudo-obstruction ("ileus") of the colon). Usually seen in hospitalized/debilitated patients. May be related to narcotics, electrolyte deficiencies, possibly from chronic constipation. Also

reported following spinal surgery/trauma, spinal/epidural anesthesia, spinal metastases, & myelography[166]

Unintended durotomy

Unintentional opening of the dura during spinal surgery has an incidence of 0-14%[167].

Terminology: The terms "unintended durotomy", "incidental durotomy"[167], or even just "dural opening", have been recommended in preference to "dural tear" which may imply carelessness[156] when none was present. Dural openings have been associated with one or more alleged complications or sequelae in medical malpractice suits involving surgery on the lumbar spine.

The injury: By itself, opening the dura intentionally or otherwise is not expected to have a deleterious effect on the patient[156, 168]. In fact, dural opening is often a standard part of the operation for intradural disc herniation[169], tumors, etc. Although not frequent, (for incidence, *see above*) unintended durotomy is not an unusual occurrence, and alone, is not considered an act of malpractice. However, it may result from an event or events that produce more serious injuries. These events and injuries should be dealt with on their own merits.

Possible sequelae include those listed in *Table 18-14*. A CSF leak may produce "spinal headache" with its associated symptoms (*see page 58*), and if it breaches the skin it may be a risk factor for meningitis. Pain or sensory/motor deficits may be associated with injuries to nerve roots or delayed herniation of nerve roots through the dural opening.

Etiologies: For incidence, *see above*. Potential causes are many, and include[156]: unanticipated anatomic variations, adhesion of the dura to removed bone, slippage of an instrument, an obscured fold of dura caught in a rongeur or curette, thinning of the dura in cases of long-standing stenosis, and the possibility of a delayed CSF leak caused by perforation of the dura when it expands onto a surgically created spicule of bone[170]. The risk may be increased with anterior decompression for OPLL, with revision surgery, and with the use of high-speed drills[167].

Table 18-14 Possible sequelae of dural opening

Well documented
1. CSF leak
A. contained: pseudomeningocele

B. external: CSF fistula
2. herniation of nerve roots thorough opening
3. associated nerve root contusion, laceration or injury to the cauda equina
4. CSF leak collapses the thecal sac and may increase blood loss from epidural bleeding
Less well documented
1. arachnoiditis
2. chronic pain
3. bladder, bowel and/or sexual dysfunction

Treatment: If the opening is recognized at the time of surgery, watertight primary closure (with or without patch graft) should be attempted with nonabsorbable suture if at all possible to prevent pseudomeningocele and/or CSF fistula. A cottonoid placed over the opening prevents aspiration of nerve roots[171]. Care must be taken to avoid incorporating a nerve root into the closure. Most repairs will be accomplished with no complication or sequelae to the patient. When the opening is in the far (anterior) side of the dura, consideration may be given to intradural repair accessed through a posterior durotomy which is subsequently closed (this may risk additional injury to the nerve roots). Biocompatible fixatives (e.g. fibrin glue[167]) may be used to supplement primary closure.

Primary repair may be impossible in some situations (e.g. when the opening cannot be found or accessed, as is sometimes the case when it occurs on the nerve root sleeve) and alternatives here include placement of a fat or muscle graft over the suspected leak site, use of a the patient's own blood for a "blood patch" (one technique is to have the anesthesiologist draw ≈ 5-10 ml of the patient's blood from an arm vein, keeping it in the syringe for several minutes until it starts to coagulate, and then to have the anesthesiologist inject the blood onto the dura), use of gelfoam, fibrin glue… Some recommend that the wound not be drained post-op, with a water-tight closure of fascia, fat, and skin to add to the barrier. Others use a subcutaneous drain or epidural catheter. CSF diversionary procedures (e.g. through a drain inserted 1 or more levels away) may also be used.

Although bed rest **x** 4-7 days is often advocated to reduce symptoms and facilitate healing, when watertight closure has been achieved, normal post-op mobilization is not associated with a high failure rate (bed rest is recommended if symptoms develop)[167].

In one report of 8 patients with leaks that appeared post-op, re-operation was avoided when treated by resuturing the skin under local anesthesia, followed by bed rest in slight Trendelenburg position (to reduce pressure on the leakage site), broad spectrum antibiotics and antibiotic ointment over the skin incision, and daily puncture and drainage of the subcutaneous collection[172].

For other treatment measures for H/A associated with CSF leak, *see page 59*.

POST-OP CARE

Post-op orders

The following are guidelines for post-operative orders for a lumbar laminectomy without intraoperative complications; variations between surgeons and institutions must be taken into consideration:

1. admit post-anesthesia recovery (PAR) unit
2. vital signs on the nursing unit: q 2° **x** 4 hrs, q 4° **x** 24°, then q 8°
3. activity: up with assist, advance as tolerated
4. nursing care
   A. I's & O's
   B. intermittent catheterization q 4-6° PRN no void
   C. *optional*: TED hose (may reduce risk of DVT) or PCB
   D. *optional (if drain used):* empty drain q 8° and PRN
5. diet: clear liquids, advance as tolerated
6. IV: D5 1/2 NS + 20 mEq KCl/l @ 75 ml/hr, D/C when tolerating PO well (after antibiotics D/C'd if prophylactic antibiotics are used)
7. meds
   A. laxative of choice **(LOC)** PRN
   B. sodium docussate (e.g. Colace®) 100 mg PO BID when tolerating PO (stool softener, does not substitute for LOC)
   C. *optional:* prophylactic antibiotics if used at your institution
   D. acetaminophen (Tylenol®) 650 mg PO or PR q 3° PRN
   E. *narcotic analgesic*
   F. *optional*: steroids are used by some surgeons to reduce nerve-root irritation from surgical manipulation
8. labs
   A. *optional (if significant blood loss during surgery):* CBC

Post-op check

In addition to routine, the following should be checked:

❑ 1. strength of lower extremities, especially muscles relevant to nerve root, e.g. gastrocnemius for L5-S1 surgery, EHL for L4-5 surgery…

❑ 2. appearance of dressing: look for signs of excessive bleeding, CSF leak…

❑ 3. signs of **cauda equina syndrome** (*see page 446*), e.g. by post-op spinal epidural hematoma:

A. loss of perineal sensation ("saddle anesthesia")

B. inability to void: may not be not unusual after lumbar laminectomy, more concerning if accompanied by loss of perineal sensation

C. pain out of the ordinary for the post-op period

D. weakness of multiple muscle groups

Any new neurologic deficit should prompt rapid evaluation for spinal epidural hematoma[162] **(EDH)**. Delayed deficits may be due to EDH or epidural abscess. Post-op films in the recovery room can rule out graft or hardware malposition for fusions or instrumentation procedures, or changes in alignment. The diagnostic test of choice is MRI. If contraindicated or not available, CT/myelography may be indicated. An extradural defect immediately post-op suggests EDH.

Outcome of surgical treatment

In a series of 100 patients undergoing discectomy, at 1 year post-op 73% had complete relief of leg pain and 63% had complete relief of back pain; at 5-10 years the numbers were 62% for each category[90]. At 5-10 years post-op, only 14% felt that the pain was the same or worse than pre-op (i.e. 86% felt improved), and 5% qualified as having a **failed back surgery syndrome** (a heterogeneous not-precisely defined term, here meaning not returned to work, requiring analgesics, receiving worker's compensation, see *Failed back surgery syndrome*, page 457).

Attempts to measure relative merits of conservative treatment vs. surgery have failed. The recent SPORT study[173, 174] suffered from significant selection bias since patients were allowed to crossover to the other arm of the study and thus more nearly approximated the current methodology of surgical selection than an actual RCT[175]. Earlier attempts at randomized trials also suffered from methodological flaws[89]. Conclusions that can be drawn from these studies[175]: most patients with manageable or improving pain and less disability typically choose conservative treatment and most have improvement in symptoms, whereas patients with severe, persistent or worsening pain and/or neurologic deficit are more likely to choose surgery with a resultant excellent outcome.

In patients with a diminished knee-jerk or ankle-jerk pre-op, 35% and 43% (respectively) still had reduced reflexes 1 year post-op[95]; reflexes were lost post-

op in 3% and 10% respectively. The same study found that motor loss was improved in 80%, aggravated in 3%, and was newly present in 5% post-op; and that sensory loss was improved in 69% and was worsened in 15% post-op.

Foot drop: severe or complete paralysis of ankle dorsiflexion occurs in 5-10% of HLD, and about 50% of cases recover with or without treatment. Discectomy does not improve the outcome, especially in cases of painless foot drop[110].

Recurrent disc herniation: (*see page 460*)

HERNIATED UPPER LUMBAR DISCS (LEVELS L1-2, L2-3, & L3-4)

L4-5 & L5-S1 herniated lumbar discs **(HLD)** account for most cases of HLD (realistically ≈ 90%, possibly as high as 98%[94]). 24% of patients with HLD at L3-4 have a past history of a HLD at L4-5 or L5-S1, suggesting a generalized tendency towards disc herniation. In a series of 1,395 HLDs, there were 4 at L1-2 (0.28% incidence), 18 at L2-3 (1.3%), and 51 at L3-4 (3.6%)[176].

PRESENTATION

Typically presents with LBP, onset following trauma or strain in 51%. With progression, paresthesias and pain in the anterior thigh occur, with complaints of leg weakness (especially on ascending stairs).

SIGNS

Quadriceps femoris was the most common muscle involved, demonstrating weakness and sometimes atrophy.

Straight leg raising was positive in only 40%. Psoas stretch test was positive in 27%. Femoral stretch test may be positive (*see page 444*).

50% had reduced or absent knee jerk; 18% had ankle jerk abnormalities; reflex changes were more common with L3-4 HLD (81%) than L1-2 (none) or L2-3 (44%).

EXTREME LATERAL LUMBAR DISC HERNIATIONS

Definition: herniation of a disc at (**foraminal disc herniation**) or distal to (**extraforaminal disc herniation**) the facet (some authors do not consider foraminal disc herniation to be "extreme lateral"). See *Figure 18-3*.

Incidence (*see Table 18-15*): 3-10% of herniated lumbar discs **(HLD)** (series with higher numbers[177] include some HLD that are not truly *extreme* lateral).

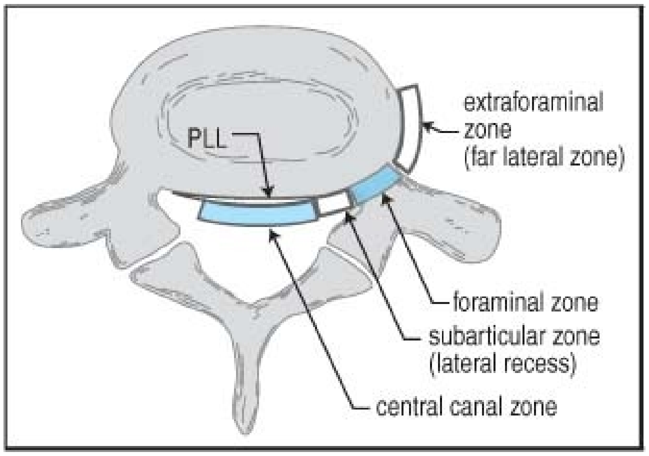

Figure 18-3 Zones of lumbar disc herniation

Differs from the more common central and subarticular HLD in that:

- the nerve root involved is usually the one exiting at that level (c.f. the root exiting at the level below)
- straight leg raising **(SLR)** is negative in 85-90% of cases ≥ 1 week after onset (excluding double herniations; ≈ 65% will be negative if double herniations are included); may have positive femoral stretch test (*see page 444*)
- pain is reproduced by lateral bending to the side of herniation in 75%
- myelography alone is rarely diagnostic (usually requires CT[178, 179] or MRI) subarticular
- higher incidence of extruded fragments (60%)
- higher incidence of double herniations on the same side at the same level (15%)
- pain tends to be more severe (may be due to fact that the dorsal root ganglion may be compressed directly) and often has more of a burning dysesthetic quality

Table 18-15 Incidence of extreme lateral HLD by level*

Disc level	No.	%
L1-2	1	1%
L2-3	11	8%
L3-4	35	24%
L4-5	82	60%
L5-S1	9	7%

* series of 138 cases[177]

Occurs most commonly at L4-5 and next at L3-4 (*see Table 18-15*), thus L4 is the most common nerve involved and L3 is next. With a clinical picture of an upper lumbar nerve root compression (i.e. radiculopathy with negative SLR), chances are ≈ 3 to 1 that it is an extremely lateral HLD rather than an upper lumbar disc herniation.

PRESENTATION

Quadriceps weakness, reduction of patellar reflex, and diminished sensation in the L3 or L4 dermatome are the most common findings.

Differential diagnosis includes:

1. lateral recess stenosis or superior articular facet hypertrophy
2. retroperitoneal hematoma or tumor
3. diabetic neuropathy (amyotrophy): *see page 796*
4. spinal tumor
   A. benign (schwannoma or neurofibroma)
   B. malignant tumors
   C. lymphoma
5. infection
   A. localized (spinal epidural abscess)
   B. psoas muscle abscess
   C. granulomatous disease
6. spondylolisthesis (with pars defect)
7. compression of conjoined nerve root
8. on MRI, enlarged foraminal veins may mimic extreme lateral disc herniation

RADIOGRAPHIC DIAGNOSIS

Radiographic diagnosis may be elusive, and up to one third are initially missed[180]. However, if actively sought, many asymptomatic far-lateral disc herniations may be demonstrated on CT or MRI.

Myelography: fails to disclose the pathology even with water soluble contrast in 87% of cases due to the fact that the nerve root compression occurs distal to the nerve root sleeve (and therefore beyond the reach of the dye)[181].

CT scan[179]: reveals a mass displacing epidural fat and encroaching on the intervertebral foramen or lateral recess, compromising the emerging root. Or,

may be lateral to foramen. Sensitivity is ≈ 50% and is similar with *post-myelographic* CT[181]. Post-discography CT[182] may be the most sensitive test (94%)[181].

MRI: similar sensitivity to post-myelographic CT. Sagittal views through the neural foramen may help demonstrate the disc herniation[180]. MRI may have ≈ 8% false positive rate due to presence of enlarged foraminal veins that mimic extreme lateral HLD[183].

SURGICAL TREATMENT

NB: compression of the dorsal root ganglion may result in a slower recovery from discectomy and overall less satisfying outcome than with the more commonplace para-median disc herniation.

Foraminal discs

Usually requires mesial facetectomy to gain access to the region lateral to the dural sac without undue retraction on nerve root or cauda equina. Caution: total facetectomy combined with discectomy may result in a high incidence of instability (total facetectomy alone causes ≈ 10% rate of slippage), although other series found this risk to be lower (≈ 1 in 33[184, 185]). An alternative technique is to remove just the lateral portion of the superior articular facet below[186]. Endoscopic techniques may be well suited for herniated discs in this location[187].

Discs herniated beyond (lateral to) the foramen

Numerous approaches are used, including:

1. traditional **midline hemilaminectomy**: the ipsilateral facet must be partially or completely removed. The safest way to find the exiting nerve root is take the laminectomy of the inferior portion of the upper vertebral level (e.g. L4 for a L4-5 HLD) high enough to expose the nerve root axilla, and then follow the nerve laterally through the neural foramen by removing facet until the HLD is identified
2. **lateral approach** (i.e. extra-canal) through a paramedian incision[188]. Advantages: the facet joint is preserved (facet removal combined with discectomy may lead to instability), muscle retraction is easier. Disadvantages: unfamiliar approach for most surgeons and the nerve cannot be followed medial to lateral. A localizing x-ray is taken with a

spinal needle. A 4-5 cm vertical skin incision is made 3-4 cm lateral to the midline on the side of the disc herniation. The incision is taken down to the thoracolumbar fascia and the subcutaneous tissue is dissected off the fascia. Above L4, one may palpate the groove between multifidus (medial) and long-issimus (lateral), where the fascia is incised. The facet joint is palpated, and blunt dissection is used to gain access to the lateral facet joint and transverse processes above and below the level of the disc herniation. The correct level is confirmed on x-ray using a probe as a marker. The intertransversarius muscle and fascia are divided. Care must be taken to avoid mechanical and electrocautery injury to the nerve and dorsal root ganglion (which lies immediately beneath the intertransverse ligament). The radicular artery, vein, and nerve root are located just beneath the transverse processes, usually slightly medial to this position. The nerve root hugs the pedicle of the level above as it exits the neural foramen (palpating this e.g. with a dental dissector helps locate it), and it may be splayed over the herniated disc fragment. If more medial exposure is necessary, the lateral facet joint may be resected. The HLD is removed. Additional removal of disc material from the disc space may be performed with down-biting pituitary rongeurs. Extracanal approach to L5-S1 requires removal of part of the sacral ala in order to access the space caudal to the L5 transverse process

DISC HERNIATIONS IN PEDIATRICS

Less than one percent of surgery for herniated lumbar disc is performed on patients between the ages of 10 and 20 yrs (one series at Mayo found 0.4% of operated HLD in patients < 17 yrs age[189]). These patients often have few neurologic findings except for a consistently positive straight leg raising test[190]. Herniated disc material in youths tends to be firm, fibrous and strongly attached to the cartilaginous end-plate unlike the degenerated material usually extruded in adult disc herniation. Plain radiographs disclosed an unusually high frequency of congenital spine anomalies (transitional vertebra, hyperlordosis, spondylolisthesis, spina bifida…). 78% did well after their first operation[189].

INTRADURAL DISC HERNIATION

Herniation of a fragment of disc into the thecal sac, or into the nerve root sleeve (the latter sometimes referred to as “intraradicular” disc herniation) has

been recognized with a reported incidence of 0.04-1.1% of disc herniations[169, 191]. Although it may be suspected on the basis of pre-op myelography or MRI, the diagnosis is rarely made preoperatively[191]. Intraoperatively, it may be suggested by the impression of a tense firm mass within the nerve root sleeve or by the negative exploration of a level with obvious clinical signs and clear cut radiographic abnormalities (after verifying that the correct level is exposed).

Surgical treatment:

Although a surgical dural opening may be utilized[169], others have found this to be necessary in a minority of cases[192].

INTRAVERTEBRAL DISC HERNIATION

AKA Schmorl's node or nodule. AKA Schmor's (no "l") nodule AKA Geipel hernia[193]. Disc herniation through the cartilaginous end plate into the cancellous bone of the vertebral body **(VB)** (AKA intraspongious disc herniation). Often an incidental finding on xray or MRI. Clinical significance is controversial. May produce low back pain initially that lasts ≈ 3-4 months after onset. Diffuse displacement (as may be seen in osteoporosis) is sometimes referred to as a **balloon disc**[5].

Clinical findings

During the acute (symptomatic) phase, patients may exhibit LBP that is aggravated by weight bearing and movement. There may be tenderness to percussion or manual compression over the involved segment.

Table 18-16 MRI signal intensity in Schmorl's nodes*

Lesion	T1WI	T2WI
symptomatic (acute)	low	high
asymptomatic (chronic)	high†	low†

* signal intensity in surrounding marrow

† the same as normal marrow

Radiographic findings

Plain x-ray: ≤ 33% may be seen on plain x-rays[194]. They may not be detectable acutely until sclerotic osseous bone casting develops.

MRI: the extrusion of disc material into the VB is easily appreciated on sagittal images. It has been suggested[195] that acute (symptomatic) lesions may appear differentiated from chronic (asymptomatic) lesions by the presence of MRI findings of inflammation in the bone marrow immediately surrounding the node as outlined in *Table 18-16*.

Treatment

Conservative treatment is indicated, usually consisting of non-steroidal anti-inflammatory drugs (NSAIDs). Occasionally stronger pain medication and/or lumbar bracing may be required. Surgery is rarely indicated.

Outcome

With conservative treatment, symptoms generally resolve within 3-4 months of onset (as with most vertebral body fractures).

JUXTAFACET CYSTS OF THE LUMBAR SPINE

The term juxtafacet cyst **(JFC)** was originated by Kao et al.[196] and includes both **synovial cysts** (those having a synovial lining membrane) and **ganglion cysts** (those lacking synovial lining) adjacent to a spinal facet joint or arising from the ligamentum flavum. Distinction between these two types of cysts may be difficult without histology (*see below*) and is clinically unimportant[197].

JFC occur primarily in the lumbar spine (although cysts in the cervical[198-200] and thoracic[201] spine have been described). They were first reported in 1880 by von Gruker during an autopsy[202], and were first diagnosed clinically in 1968[203]. The etiology is unknown (possibilities include: synovial fluid extrusion from the joint capsule, latent growth of a developmental rest, myxoid degeneration and cyst formation in collagenous connective tissue…), increased motion seems to have a role in many cysts, and the role of trauma in the pathogenesis is debated[199, 204] but probably plays a role in a small number (≈ 14%)[205]. JFC are relatively rare, only 3 cases were identified in a series of 1,500 spinal CT exams[206], but the frequency of diagnosis may be on the rise due to the widespread use of MRI and an increasing awareness of the condition.

Clinical

The average age was 63 years in one series[205] and 58 years in a review of 54

cases in the literature[207] (range: 33-87) with a slight female preponderance in both series. Most occur in patients with severe spondylosis and facet joint degeneration[208], 25% had degenerative spondylolisthesis[205]. L4-5 is the most common level[205, 209]. They may be bilateral. Pain is the most common symptom, and is usually radicular. Some JFC may contribute to canal stenosis and can produce neurogenic claudication[210] (*see page 477*) or on occasion a cauda equina syndrome. Symptoms may be more intermittent in nature than with firm compressive lesions, such as HLD. A sudden exacerbation in pain may be due to hemorrhage within the cyst. Some JFC may be asymptomatic[211].

Differential diagnosis (also see *Differential diagnosis, Sciatica* on page 1188). Differentiating JFC from other masses relies largely on the appearance and location. Other distinguishing features include:

1. neurofibroma: unlikely to be calcified
2. free fragment of HLD: not cystic in appearance
3. epidural or nerve root metastases: not cystic
4. dural subarachnoid root sleeve dilatation: see *Spinal meningeal cysts*, page 509
5. arachnoid cyst (from arachnoid herniation through a dural defect): not associated with facet joint, margins thinner than JFC[212]
6. perineurial cysts (Tarlov's cyst): arise in space between perineurium and endoneurium, usually on sacral roots[213], occasionally show delayed filling on myelography. Usually associated with remodelling of adjacent bone

Pathology

Cyst walls are composed of fibrous connective tissue of varying thickness and cellularity. There is usually no signs of infection or inflammation. There may be a synovial lining[207] (synovial cyst) or it may be absent[208] (ganglion cyst). The distinction between the two may be difficult[197], possibly owing in part to the fact that fibroblasts in ganglion cysts may form an incomplete synovial-like lining[214]. Proliferation of small venules is seen in the connective tissue. Hemosiderin staining may be present, and may or may not be associated with a history of trauma[205].

Evaluation

Identifying a JFC pre-op helps the surgeon, as the approach differs slightly from that for HLD, and the cyst might otherwise be missed or unknowingly

deflated and unnecessary time wasted afterwards trying to find a compressive lesion. Or, the unwitting surgeon may misinterpret the cyst as a "transdural disc extrusion" and needlessly open the dura. Pre-op diagnoses were incorrect in 30% of operated cases of JFC[205].

Myelography: posterolateral filling defect (whereas most discs are situated anteriorly, an occasional fragment may migrate posterolaterally, whereas a JFC will always be posterolateral), often with a round extradural appearance.

CT scan: shows a low density epidural cystic lesion typically with a posterolateral juxtaarticular location. Some have calcified rim[211], and some may have gas within[215]. Erosion of bony lamina is occasionally seen[209, 216].

MRI: variable findings (may be due to differing composition of cyst fluid: serous vs. proteinaceous[217]). Unenhanced signal characteristics of non-hemorrhagic JFC are very similar to CSF. Hemorrhagic JFC are hyperintense. May be missed on sagittal imaging without contrast. Axial images may better demonstrate JFC. Gadolinium enhancement increases the sensitivity[208]. MRI usually misses bony erosion.

Treatment

Optimal treatment is not known. There is one case report of a cyst that resolved spontaneously[206]. If symptoms persist with conservative treatment, some promote cyst aspiration or facet injection with steroids[218], while most advocate surgical excision of the cyst.

Surgical treatment considerations: The cyst may be adherent to the dura. The cyst may also collapse during the surgical approach and may be missed. A JFC may serve as a marker for possible instability and should prompt an evaluation for the same. Some argue for performing a fusion since JFC may arise from instability, however, it appears that fusion is not required for a good result in many cases[218]. Therefore it is suggested that consideration for fusion be made on the basis of any instability and not merely on the basis of the presence of a JFC.

Minimally invasive spine surgery (MISS) has also been used for removal[219], long-term follow-up is lacking. A 15 mm entry incision is made 1.5 cm lateral to midline.

Following surgical treatment, symptomatic JFCs may recur or may develop on the contralateral side[205].

FAILED BACK SURGERY SYNDROME

Definition: failure to improve satisfactorily following back surgery (for herniated intervertebral disc, laminectomy for stenosis…). These patients often require analgesics and are unable to return to work. The failure rate for lumbar discectomy to provide satisfactory long-term pain relief is ≈ 8-25%[220]. Pending legal or worker's compensation claims were the most frequent deterrents to a good outcome[157].

Factors that may cause or contribute to the failed back syndrome:

1. incorrect initial diagnosis
   A. inadequate pre-op imaging
   B. clinical findings not correlated with abnormality demonstrated on imaging
   C. other causes of symptoms (sometimes in the presence of what was considered to be an appropriate lesion on imaging studies which may have been asymptomatic): e.g. trochanteric bursitis, diabetic amyotrophy…
2. continued nerve root or cauda equina compression caused by:
   A. residual compression (retained disc material, osteophytes…)
   B. recurrent pathology at same level: disc reherniation at the same level (usually have pain-free interval > 6 mos post-op (*see page 460*)) or restenosis (over many years[221] - was more common with midline fusions))
   C. adjacent level pathology: disc herniation or stenosis[221]
   D. compression of nerve root by peridural **scar** (granulation) tissue (*see below*)
   E. pseudomeningocele
   F. epidural hematoma
   G. conjoined nerve roots with compression at another level or in atypical location
   H. segmental instability: 3 patterns[222, 1]) lateral rotational instability, 2) postop spondylolisthesis, 3) post-op scoliosis
3. permanent nerve root injury from the original disc herniation or from surgery, includes deafferentation pain which is usually constant and burning or ice cold
4. adhesive **arachnoiditis**: responsible for 6-16% of persistent symptoms in post-op patients[223] (*see below*)
5. discitis: usually produces exquisite back pain 2-4 weeks post-op (*see page*

383)

6. spondylosis
7. other causes of back pain unrelated to the original condition: paraspinal muscle spasm, myofascial syndrome… Look for trigger points, evidence of spasm
8. post-op reflex sympathetic dystrophy **(RSD)**: *see page 450*
9. "non-anatomic factors": poor patient motivation, secondary gains, drug addiction, psychological problems… (see *Psychosocial factors*, page 436)

ARACHNOIDITIS (AKA ADHESIVE ARACHNOIDITIS)

Inflammatory condition of the lumbar nerve roots. Actually a misnomer, since adhesive arachnoiditis is really an inflammatory process or fibrosis that involves all three meningeal layers (pia, arachnoid, and dura). Many putative "risk factors" have been described for the development of arachnoiditis, including[224]:

1. spinal anesthesia: either due to the anesthetic agents *or* to detergent contaminants on the syringes used for same
2. spinal meningitis: pyogenic, syphilitic, tuberculous
3. neoplasms
4. myelographic contrast agents: less common with currently available water soluble contrast agents
5. trauma
   A. post-surgical: especially after multiple operations
   B. external trauma
6. hemorrhage
7. idiopathic

Radiographic findings in arachnoiditis

NB: Radiographic evidence of arachnoiditis may also be found in asymptomatic patients[224]. Arachnoiditis must be differentiated from tumor: the central adhesive type (*see below*) may resemble CSF seeding of tumor, and myelographic block may mimic intrathecal tumor.

Myelogram: May demonstrate complete block, or clumping of nerve roots. One of many myelographic classification systems[225] for arachnoiditis is shown in *Table 18-17*.

MRI:[3] patterns on MRI[226, 227]:

1. central adhesion of the nerve roots into 1 or 2 central "cords"
2. "empty thecal sac" pattern: roots adhere to meninges around periphery, only CSF signal is visible intrathecally
3. thecal sac filled with inflammatory tissue, no CSF signal. Corresponds with myelographic block and candle-dripping appearance

Enhancement: acute arachnoiditis may enhance. Chronic arachnoiditis usually does not enhance with gadolinium as much as tumor.

Table 18-17 Myelographic classification of arachnoiditis

Type	Description
1	unilateral focal filling defect centered on the nerve root sleeve adjacent to disc space
2	circumferential constriction around thecal sac
3	complete obstruction with "stalactites" or "candle guttering", "candle-dripping", or "paint-brush" filling defects
4	infundibular cul-de-sac with loss of radicular striations

Peridural scar

Although peridural scar is frequently blamed for causing recurrent symptoms[228, 229], there has been no proof of correlation[230]. Peridural fibrosis is an inevitable sequelae to lumbar disc surgery. Even patients who are relieved of their pain following discectomy develop some scar tissue post-op[231]. Although it has been shown that if a patient has recurrent radicular pain following a lumbar discectomy there is a 70% chance that extensive peridural scar will be found on MRI[230], this study also showed that on post-op MRIs at 6 months, 43% of patients will have extensive scar, but 84% of the time this will be asymptomatic[232]. Thus, one must use clinical grounds to determine if a patient with extensive scar on MRI is in the 16% minority of patients with radicular symptoms attributable to scar[232].

For a discussion of measures to reduce peridural scarring, *see page 448*.

Radiologic evaluation

Patients with only persistent low back or hip pain without a strong radicular component, with a neurologic exam that is normal or unchanged from pre-op, should be treated symptomatically. Patients with signs or symptoms of recurrent radiculopathy (positive SLR is a sensitive test for nerve root compression),

especially if these follow a period of apparent recovery, should undergo further evaluation.

It is critical to differentiate residual/recurrent disc herniation from scar tissue and adhesive arachnoiditis as surgical treatment has generally poor results with the latter two (see *Treatment of failed back surgery syndrome* below).

MRI without and with IV gadolinium

Diagnostic test of choice. The best exam for detecting residual or recurrent disc herniation, and to reliably differentiate disc from scar tissue. Pre-contrast studies with T1WI and T2WI yields an accuracy of ≈ 83%, comparable to IV enhanced CT[233, 234]. With the addition of gadolinium, using the protocol below yields 100% sensitivity, 71% specificity, and 89% accuracy[235]. May also detect adhesive arachnoiditis (*see above*). As scar becomes more fibrotic and calcified with time, the differential enhancement with respect to disc material attenuates and may become undetectable at some point, ≈ 1-2 years postop[234] (some scar continues to enhance for > 20 yrs).

Recommended protocol[235]

Get pre-contrast T1WI and T2WI. Give 0.1 mmol/kg gadolinium IV. Obtain T1WI images within 10 minutes (early post-contrast). No benefit from post-contrast T2WI.

Findings on unenhanced MRI

Signal from a HLD becomes more intense as the sequence is varied from T1WI → T2WI, whereas scar tissue becomes less intense with this transition. Indirect signs (also applicable to CT):

1. mass effect: a nerve root is displaced away from disc material, whereas it may be retracted toward scar tissue by adherence to it
2. location: disc material tends to be in contiguity with the disc interspace (best seen on sagittal MRI)

Findings on enhanced MRI

On *early* (≤ 10 mins post-contrast) T1WI images: scar enhances inhomogeneously, whereas disc does not enhance at all. A nonenhancing central area surrounded by irregular enhancing material probably represents disc wrapped in scar. Venous plexus also enhances, and may be more pronounced

when it is distorted by disc material, but the morphology is easily differentiated from scar tissue in these cases.

On *late* (> 30 mins post-contrast) T1WI: scar enhances homogeneously, disc had variable or no enhancement. Normal nerve roots do not enhance even on late images.

CT scan without and with IV (iodinated) contrast

Unenhanced CT scan density measurements are unreliable in the postoperative back[236]. Enhanced CT is only fairly good in differentiating scar (enhancing) from disc (un-enhancing with possible rim enhancement). Accuracy is about equal to unenhanced MRI.

Myelography, with post-myelographic CT

Postoperative myelographic criteria alone are unreliable for distinguishing disc material from scar[224, 237]. With the addition of CT scan, neural compression is clearly demonstrated, but scar still cannot be reliably distinguished from disc.

Myelography (especially with post-myelographic CT) is very capable of demonstrating arachnoiditis[237] (*see above*).

Plain LS X-rays

Generally helpful only in cases of instability, malalignment, or spondylosis[237]. Flexion/extension views are most helpful when trying to demonstrate instability.

Treatment of failed back surgery syndrome

For treatment of intervertebral disc-space infection, see *Discitis*, page 383.

Symptomatic treatment

Recommended for patients who do not have radicular signs and symptoms, or for most patients demonstrated to have scar tissue or adhesive arachnoiditis on imaging. As in other cases of non-specific LBP treatment includes: short-term bed rest, analgesics (non-narcotic in most cases), anti-inflammatory medication (non-steroidal, and occasionally a short course of steroids), and physical therapy.

Surgery

Reserved for those with recurrent or residual disc herniation, segmental

instability, or patients with a pseudomeningocele. Patients with post-op spinal instability should be considered for spinal fusion[222] (*see page 440*).

In most series with sufficient follow-up, success rates after reoperation are lower in patients with only epidural scar (as low as 1%) compared to those patients with disc and scar (still only ≈ 37%)[220]. An overall success rate (> 50% pain relief for > 2 yrs) of ≈ 34% was seen in one series[229], with better results in patients that were young, female, with good results following previous surgery, a small number of previous operations, employment prior to surgery, predominantly radicular (cf axial) pain, and absence of scar requiring lysis.

In addition to the absence of disc material, factors associated with poor outcome were: sensory loss involving more than one dermatome, and patients with past or pending compensation claims[220, 238].

Arachnoiditis: Surgery for carefully selected patients with arachnoiditis (those with mild radiographic involvement (Types 1 & 2 in *Table 18-17*), and < 3 previous back operations)[225] has met with moderate success (although in this series, no patient returned to work). Approximate success rate in other series[239, 240]: 50% failure, 20% able to work but with symptoms, 10-19% with no symptoms. Surgery consists of removal of extradural scar enveloping the thecal sac, removing any herniated disc fragments, and performing foraminotomies when indicated. Intradural lysis of adhesions is <u>not</u> indicated since no means for preventing reformation of scar has been identified[240].

RECURRENT HERNIATED LUMBAR DISC

Rates quoted in the literature range from 3-19% with the higher rates usually in series with longer follow-up[241]. In an individual series with 10 year mean F/U, the rate of recurrent disc herniation was 4% (same level, either side), one third of which occurred during the 1st year post-op (mean: 4.3 yrs)[157]. A <u>second</u> recurrence at the same site occurred in 1% in another series[241] with mean F/U of 4.5 yrs. In this series[241], patients presenting for a second time with disc herniation had a recurrence at the same level in 74%, but 26% had a HLD at another level. Recurrent HLD occurred at L4-5 more than twice as often as L5-S1241.

It is often possible for a smaller amount of recurrent herniated disc to cause symptoms than in a "virgin back", due to the fact that the nerve root is often fixated by scar tissue and has little ability to deviate away from the fragment[150].

TREATMENT

Initial recommended treatment is as with a first time HLD. Nonsurgical treatment should be utilized in the absence of progressive neurologic deficit, cauda equina syndrome **(CES)** or intractable pain.

Surgical treatment

Disagreement occurs regarding optimal treatment. See *PRACTICE GUIDELINE 18-5*, page 440.

Surgical outcome:

As with first time HLD, the outcome from surgical treatment is worse in worker's compensation cases and in patients undertaking litigation, only ≈ 40% of these patients benefit[241, 242]. A worse prognosis is also associated with: patients with < 6 mos relief after their first operation, cases where fibrosis without recurrent HLD is found at operation.

Spinal cord stimulation

One study actually showed a better response rate to spinal cord stimulation than to reoperation[243]. Since surgery for recurrent HLD carries a higher risk of dural and nerve root injury, and a lower success rate than first time operations, this may be a viable option for some patients.

18.3.2. Cervical disc herniation

CLINICAL ASPECTS

The following facts explain the findings in herniated cervical disc **(HCD)**:

1. in the cervical region, the nerve root exits <u>above</u> the pedicle of its like-numbered vertebra (opposite to the situation in the lumbar spine, due to the fact that there are 8 cervical nerve roots and only 7 cervical vertebrae)
2. each root exits passes through its neural foramen in close relation to the undersurface of the pedicle
3. the intervertebral disc space is located close to the inferior portion of the pedicle (unlike the lumbar region)

CERVICAL NERVE ROOT SYNDROMES (CERVICAL RADICULOPATHY)

Due to the facts listed above, a HCD usually impinges on the nerve exiting from the neural foramen at the level of the herniation (e.g. a C6-7 HCD usually

causes C7 radiculopathy). This gives rise to the characteristic cervical nerve root syndromes shown in *Table 18-18*.

Some clinical specifics:

C4 radiculopathy is not common, and may produce nonradiating axial neck pain. Left C6 radiculopathy (e.g. from C5-6 HCD) occasionally presents with pain simulating an MI (pseudo-angina). C8 and T1 nerve root involvement may produce a partial Horner's syndrome.

The most common scenario for patients with herniated cervical disc is that the symptoms were present upon awakening in the morning, without identifiable trauma or stress[244].

Table 18-18 Cervical disc syndromes

	— Level of herniated cervical disc —			
	C4-5	**C5-6**	**C6-7**	**C7-T1**
% of cervical discs	2%	19%	69%	10%
compressed root	C5	C6	C7	C8
reflex diminished	deltoid & pectoralis	biceps & brachioradialis	triceps	finger-jerk*
motor weakness	deltoid	forearm flexion	forearm ext (wrist drop)	hand intrinsics
paresthesia & hypesthesia	shoulder	upper arm, thumb, radial forearm	fingers 2 & 3, all fingertips	fingers 4 & 5

* not everyone has a finger flexor reflex. Description: gently lift the fingertips of the patient's pronated hand and tap the underside of the fingers with a reflex hammer. When present, fingers flex in response

Differential diagnosis: *see page 1197*.

Cervical myelopathy and SCI due to cervical disc herniation

Acute cord compression presenting with myelopathy or SCI (including complete SCI and incomplete syndromes, especially central cord syndrome (*see page 948*) and some-times Brown-Sequard syndrome[245] (*see page 950*)) is well described in association with traumatic cervical disc herniation[246]. Less commonly, these findings may occur in non-traumatic cervical disc herniation.

Signs useful in evaluating cervical radiculopathy

Almost all herniated cervical discs cause painful limitation of neck motion. Neck extension usually aggravates pain when cervical disc disease is present (a minority of patients instead exhibit pain with flexion). Some patients find relief

in elevating the arm and cupping the back or the top of the head with the hand (**abduction relief sign**, *see below* for shoulder abduction test). Lhermitte's sign (electrical shock-like sensation radiating down the spine) may be present (*see page 1198* for DDx).

Miscellaneous

The following tests were found to be specific, but not particularly sensitive in detecting cervical root compression[247]:

1. **Spurling's sign** 248: radicular pain reproduced when the examiner exerts down-ward pressure on vertex while tilting head towards symptomatic side (sometimes adding neck <u>extension</u>). Causes narrowing of the intervertebral foramen and possibly increases disc bulge. Used as a "mechanical sign" analogous to SLR for lumbar disc herniation
2. **axial manual traction**: 10-15 kg of axial traction is applied to a supine patient with radicular symptoms (pull up on patient's mandible and occiput). The reduction or disappearance of radicular symptoms is a positive finding
3. **shoulder abduction test** 249: a sitting patient with radicular symptoms lifts their hand above their head. The reduction or disappearance of radicular symptoms is a positive finding. Moderately sensitive, fairly specific[250]

EVALUATION

MRI

The study of choice for initial evaluation for herniated cervical disc **(HCD)**. Accuracy is less than water soluble contrast myelogram/CT (≈ 85-90% accuracy for MRI because of only fair to good imaging of neural foramen), but is non-invasive. For <u>myelopathy</u>, MRI is > 95% effective in diagnosing.

CT AND MYELOGRAM/CT

Indications: when MRI cannot be done, when resolution or image quality on MRI is inadequate, or when more bony detail is required. Also, to evaluate for ossification of the posterior longitudinal ligament **(OPLL)** in suspicious cases.

Plain CT: is usually good at C5-6, is variable at C6-7 (due to artifact from patient's shoulders, depending on body habitus), and is usually poor at C7-T1.

Myelogram/CT (water soluble intrathecal contrast): invasive, on rare

occasions requires overnight hospitalization. Accuracy is ≈ 98% for cervical disc disease.

TREATMENT

Over 90% of patients with acute cervical radiculopathy due to cervical disc herniation can improve without surgery[251]. The recovery period may be made more tolerable by adequate pain medication, anti-inflammatory medication (NSAIDs or short-course tapering steroids) and intermittent cervical traction (e.g. 10-15 lbs for 10-15 minutes, 2-3 **x** daily).

Surgery is indicated for those that fail to improve or those with progressive neurologic deficit while undergoing non-surgical management.

Management of myelopathy/central cord syndrome associated with acute cervical disc herniation is controversial, since the natural history is favorable in most cases. However, some patients have poor recovery and experience permanent deficits even with emergency surgery[252].

Surgical options:

1. anterior cervical discectomy: *see below*
    A. without any prosthesis or fusion
    B. combined with fusion: the most common approach
        1. without anterior cervical plating
        2. with anterior cervical plating
    C. with artificial disc (arthroplasty)
2. posterior approaches
    A. cervical laminectomy
    B. keyhole laminotomy

For practice guidelines regarding intra-op electrophysiologic monitoring for surgery for cervical radiculopathy, see *PRACTICE GUIDELINE 18-18*, page 491.

ANTERIOR CERVICAL DISCECTOMY WITH FUSION (ACDF)

Without special modifications, a routine anterior approach is limited ≈ to levels C3-7.

Advantages over posterior (nonfused) approach:

1. safe removal of osteophytes
2. fusion of disc space affords immobility (up to 10% incidence of

subluxation with extensive posterior approach)

3. only viable means of directly dealing with centrally herniated disc

Disadvantages over posterior approach: immobility at fused level may increase stress on adjacent disc spaces. If a fusion is performed, some surgeons prescribe a rigid collar (e.g. Philadelphia collar) for 6-12 weeks. Multiple level ACDF can devascularize the vertebral body (or bodies) between discectomies.

Booking the case - ACDF

Also see defaults & disclaimers (*page v*).

1. position: supine, some use halter traction with this
2. equipment:
   A. microscope (not used by all surgeons)
   B. C-arm
3. implants: graft (e.g. PEEK, cadaver bone, titanium cage…) and anterior cervical plate (optional, especially on single level ACDF)
4. neuromonitoring: (optional) some surgeons used SSEP/MEP
5. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the front of the neck to remove the degenerated disc and bone spurs, and to place a graft where the disc was, and possibly place a metal plate on the front of the spine. Some surgeons take bone from the hip to replace the removed disc
   B. alternatives: nonsurgical management, surgery from the back of the neck, artificial disc (in some cases)
   C. complications: swallowing difficulties are common but usually resolve, hoarseness of the voice (< 4% chance of it being permanent), injury to: food-pipe (esophagus), windpipe (trachea), arteries to the brain (carotid), spinal cord with paralysis, nerve root with paralysis, possible seizures with MEPs

Technique

A summary of the steps involved is included here. For C5-6, the skin incision is made at level of cricoid cartilage, for other levels, appropriate adjustments up or down may be made, sometimes with the assistance of fluoroscopy. The incision is approximately 5-6 cm horizontally, centered on the SCM. Many right handed surgeons prefer operating from the right side of the neck, although the

risk to the recurrent laryngeal nerve **(RLN)** is lower with a left sided approach (the RLN lies in a groove between the esophagus and trachea). The skin may be undermined off the platysma to permit a vertical incision in the platysma in the same orientation as its muscle fibers. Alternatively, some incise the platysma horizontally with scissors horizontally.

Dissect in tissue plane medial to SCM. For the C5-6 interspace, angle slightly cranially during dissection. For the C6-7 disc, proceed almost straight down to spine. Sweep omohyoid medially (to stay out of it and to protect the RLN). The trachea + esophagus are retracted medially. The carotid sheath + SCM are retracted laterally.

After verification of level with lateral C-spine x-ray with spinal needle in the interspace, bipolar the prevertebral fascia and medial edges of the longus coli muscles longitudinally in the midline. Self-retaining retractor blades are inserted underneath the fascia to retract the longus coli muscles laterally. The anesthesiologist is asked to deflate the cuff on the endotracheal tube and then to re-inflate it using minimal leak technique to reduce the risk of compression injury from the retractor. The disc space is incised with a 15 scalpel blade. The discectomy is performed with curettes and pituitary rongeurs; a vertebral body spreader aids the exposure. The posterior longitudinal ligament is incised, one technique is to elevate it with a sharp nerve hook and then incise it with a #11 scalpel. The subligamentous space is probed with a blunt nerve hook. The posterior lip of the VB above and below are removed with a Kerrison rongeur with a small foot-plate. Decompression of the roots is verified with the blunt nerve hook. Fusion is performed at this time if desired by placing the graft in the interspace.

For redo operations (same or different levels): approach is usually from the same side as previous operation(s) since many patients have swallowing issues post-op, and some may be due to partial recurrent laryngeal nerve injury (which can be subclinical) and which could result in a permanent need for a feeding tube if a contralateral injury occurs. If for some reason it is desired to go to the opposite side, an evaluation by an ENT physician is recommended, and should include scoping the patient to rule-out subclinical problems that could turn into major difficulties if bilateral.

To fuse or not to fuse?

Table 18-19 compares ACD (no fusion) to ACDF for radiculopathy in a number of aspects[253].

Choice of graft material:

Autologous bone (usually from iliac crest), non-autologous bone (cadaveric), bone substitutes (e.g. hydroxyapatite[254]) or synthetics (e.g. PEEK or titanium cage) filled with osteogenic material. Substitutes for autologous bone eliminate problems with the donor site (*see page 465*), but may have a higher rate of absorption. There were also cases of HIV transmission from cadaveric bone grafts in 1985, however, no further cases have been reported.

Anterior cervical plating: Recommendations for plating following ACDF are shown in *PRACTICE GUIDELINE 18-7*.

Table 18-19 Comparison of ACD to ACDF for radiculopathy[253]

Component	Assessment
Clinical outcome measures*	ACD & ACDF are equivalent (**Level C**, Class I)
Relief of arm pain	
Relief of neck pain associated with 1-level disc degeneration	Conflicting evidence which is better (Class II)
More <u>rapid</u> relief of neck and arm pain	ACDF is better than ACD (**Level D**, Class III) (functional outcomes are similar)
Maintaining foraminal or disc space height	ACDF cannot be recommended over ACD (**Level C**, Class II)
Risk of post-op kyphosis	ACDF is better than ACD (**Level C**, Class II)
Fusion rate	

* VAS, Odom's criteria, McGill pain questionnaire, SF-36

PRACTICE GUIDELINE 18-7 ANTERIOR CERVICAL PLATING

1 level ADCF: The addition of an anterior plate to an ACDF is recommended to reduce the pseudarthrosis rate and graft problems (**Level D** Class III) and to maintain lordosis (**Level C** Class II) but it does not improve clinical outcome alone (**Level B** Class II)[253]
2 level ADCF: Plating is recommended to improve arm pain. Plating does not improve other outcome parameters (**Level C** Class II)[253]

Use of bone morphogenic proteins (BMP):

PRACTICE GUIDELINE 18-8 USE OF BMP IN CERVICAL INTERBODY

GRAFTING
Current evidence does not support the *routine* use of rhBMP-2 for cervical arthrodesis (Level C Class II)[255]*

* italics added. Use with precautions (see text) may be indicated in cases with high risk of nonunion

Use of BMP in anterior cervical discectomies is not FDA approved, but has been used off-label. Complication rates as high as 23-27% have been reported (including postop swallowing or respiratory difficulties as a result of edema which is usually temporary) compared to 3% without BMP[255]. If used, it is recommended that a smaller dose be employed than in the lumbar spine (25% has been advocated) and to avoid contact of BMP with soft tissues in the neck.

POST-OP CHECK

In addition to routine, the following should be checked

❑ 1. evidence of significant post-op wound hematoma: should be first consideration in patient with airway obstruction post-op. Wound may need to be emergently opened on floor if airway is compromised, see *Carotid endarterectomy, disruption of arteriotomy closure, management* on page 1154. Also consider swelling from IJV thrombosis (rare) in differential diagnosis (*see below*)

A. respiratory distress

B. extreme difficulty swallowing: alternatively may indicate anterior extrusion of bone graft impinging upon esophagus (check lateral C-spine x-ray)

C. tracheal deviation: may be visible or may be seen on AP C-spine x-ray

❑ 2. weakness of nerve root of level operated: e.g. biceps for C5-6, triceps for C6-7

❑ 3. long tract signs (Babinski sign…) which may indicate cord compression by spinal epidural hematoma

❑ 5. hoarseness: may indicate vocal cord paresis from recurrent laryngeal nerve injury: hold oral feeding until this can be further assessed

ACDF COMPLICATIONS

Common ones listed below, see references[256, 257] for more details. The most common complication following ACDFs: swallowing difficulties (may be multifactorial).

- exposure injuries
    A. perforation of pharynx, esophagus and/or trachea: minimize by blunt retraction until longus colli is separated from its attachment to vertebrae.
        - Esophageal injuries are very difficult to manage, and require ENT involvement. The incidence may be higher with use of anterior cervical plate, and injury may not manifest until years after the fusion (may be due to repetitive motion of esophagus over the plate). Treatment of esophageal perforation is usually facilitated by plate removal
    B. vocal cord paresis: due to injury of the recurrent laryngeal nerve **(RLN)** or vagus. Incidence: **11%** temporary, **4%** permanent paresis. Symptoms include: hoarseness, breathiness, cough, aspiration, mass sensation, dysphagia, and vocal cord fatigue[258]. Avoid sharp dissection in paratracheal muscles. Some cases may be due to prolonged retraction against trachea and not to nerve division; to reduce this risk, after the self-retaining retractor is placed, have the anesthesiologist deflate the cuff on the ET tube and then inflate it to minimal leak pressure. More common with right sided approaches, primarily in the lower cervical spine (C5-6 and below) where the RLN is more vulnerable[258]
    C. vertebral artery injury: thrombosis or laceration. 0.3% incidence[257]. Treatment alternatives include: packing, direct repair by temporary clipping with aneurysms clips and repair with 8-0 prolene[259] and endovascular trapping. Risks of treating hemorrhagic complications with packing include: recurrent bleeding, AV fistula, pseudoaneurysm, arterial thrombosis[257], distal embolic CVA (primarily in cerebellum)
    D. carotid injury: thrombosis, occlusion, or laceration (usually by retraction)
    E. CSF fistula: usually difficult to repair directly. Place fascial graft beneath bone plug. Keep HOB elevated post op. Consider: dural sealant (fibrin glue, DuraSeal®…), lumbar drain
    F. Horner’s syndrome: sympathetic plexus lies within longus coli, thus do not extend dissection far laterally into these muscles

G. thoracic duct injury: in exposing lower cervical spine, primarily on left

H. thrombosis of **internal jugular vein**[260]: rare. Carries 2-3% risk of PE[261]. Treatment options: anticoagulation (oral or IV) may lower the mortality[262], SVC filter if anticoagulation is contraindicated[263], percutaneous thrombectomy[264]

- spinal cord or nerve root injuries
  A. spinal cord injury: especially risky in myelopathy due to narrowed canal. Minimize risk by penetrating the osteophyte at the lateral margin of interspace (however, this increases risk to nerve root)
  B. avoid hyperextension during intubation: anesthesiologist may need to determine patient's tolerance pre-op. Consider fiberoptic guided or awake nasotracheal intubation in extreme stenosis
  C. bone graft must be shorter than interspace depth. Exercise caution in tapping graft into position
  D. sleep induced apnea: rare but serious complications of C3-4 level operations[265]. May be associated with bradycardia & cardiorespiratory instability. Possibly due to disruption of the afferent component of the central respiratory control mechanism
- bone fusion problems
  A. failure of fusion (pseudarthrosis): *see below*
  B. anterior (kyphotic) angulation deformity: may be as high as 60% with Cloward technique (may be reduced by collar immobilization). May develop in Hirsch technique with excessive bone removal
  C. graft extrusion: 2% incidence (rarely requires re-operation unless compression of cord posteriorly, or esophagus or trachea anteriorly occurs)
  D. donor site complications: hematoma/seroma, infection, fracture of ilium, injury to lateral femoral cutaneous nerve, persistent pain due to scar, bowel perforation
- miscellaneous
  A. wound infection: incidence < 1%
  B. post-op hematoma: *see above*. Placing cervical collar in O.R. may delay recognition
  C. dysphagia and hoarseness: common. Usually transient (*see below*)
  D. adjacent level degeneration: controversial whether this represents a sequelae to altered biomechanics from surgery, or a predisposition to

cervical spondylosis[266]. Many (≈ 70%) are asymptomatic[267]

E. postoperative discomfort:
   1. globus: the sensation of a lump in throat (*see below*)
   2. nagging discomfort in neck, shoulder, and very commonly in interscapular regions (may last several months). May correlate with amount of distraction of the disc space

F. complex regional pain syndrome AKA reflex sympathetic dystrophy **(RSD)**: rarely described in the literature[268], possibly due to stellate ganglion injury (*see page 576*)

G. angioedema: massive edema of the tongue and neck[269]. A dramatic hypersensitivity reaction (not really a direct complication of ACDF, but superficially can mimic some findings of post-op hematoma). If limited to the tongue, the airway is not compromised. For treatment, *see page 125*

H. pneumothorax or hemothorax[270]: accessing C7-T1 or lower may expose the pleural apex

Dysphagia following ACDF

Symptoms: Include: difficulty swallowing (solids, liquids including saliva), pain with swallowing (odynophagia), globus (sensation of a lump in throat) and compromise of ability to protect against aspiration. Food may stick in the throat (or feel as if it is) and there may be coughing or choking.

Incidence: Early dysphagia is common. Incidence: 60%[271] in retrospective survey after noninstrumented fusion[A], 50% in prospective study[272]. At 6 months, only ≈ 5% reported moderate or severe dysphagia[272]. Surgery at multiple levels increased the risk at 1 & 2 months[272]. Decreases significantly in most cases by 6 months[272].

Etiologies: Etiologies of post-op dysphagia include:

1. post-op hematoma. If severe, may cause tracheal obstruction (*see above*)
2. post-op edema, due in part to retraction of esophagus
3. effects of general anesthesia: e.g. irritation from ET tube. Accounts for up to 23% of early symptoms[A]. Usually subsides within ≈ 24-72 hours
4. recurrent laryngeal nerve dysfunction:
   A. temporary: usually due to traction on the nerve
   B. permanent: 1.3% at 12 months[272]

5. esophageal injury
   A. at time of surgery
   B. delayed: possibly from repetitive abrasion on surgical site/hardware
6. cervical collar
   A. prevents patient from lowering jaw during swallow phase, which compromises effective glottic closure of airway
   B. may be too tight thereby directly squeezing the throat
7. protrusion of graft/hardware anterior to the vertebral bodies
   A. some protrusion is present with most anterior hardware. This may be minimized with “zero profile” instrumentation
   B. hardware failure (screw-pullout/backout/breakage, plate pullout)
   C. interbody graft migration: without anterior plate, or in conjunction with anterior plate displacement
8. excessive adhesions[273]
9. denervation of the pharyngeal plexus[273]
10. rare conditions: swelling from IJV thrombosis, angioedema

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A. dysphagia occurred in 23% in a control group undergoing unrelated lumbar spine surgery[271]

Management:

1. initial management: rule-out emergent/serious conditions (severe edema, hematoma with airway compromise, risk of aspiration)
   A. if there is significant stridor or dysphonia, especially if tracheal deviation is obvious, someone must stay with the patient as efforts are made to emergently take the patient to the O.R. for wound exploration evacuation. Consider opening the wound at the bedside if delays occur or if symptoms are severe (see *Carotid endarterectomy, disruption of arteriotomy closure, management* on page 1154). Emergent anesthesia consultation for airway protection - alert them to the likelihood of deviated trachea which challenges even the most expert at intubating
2. once emergent conditions are ruled out, early management is geared towards amelioration of symptoms
   A. advise patient to eat softer foods (temporarily avoiding steak or bread), to chew food well, to wash down dry foods with a drink. Reassure patient that most cases largely resolve with 6 months[272]

B. if significant symptoms persist > 2 weeks
   1. refer patient to ENT for laryngoscopy to rule out vocal cord paralysis (from RLN injury) or other etiologies
   2. modified barium swallow
3. persistent symptoms may be amenable to surgical intervention, including hardware removal and lysing of adhesions[273], management of esophageal perforation usually requires consultation with ENT

Pseudarthrosis (or pseudoarthrosis) following ACDF

PRACTICE GUIDELINE 18-9 ASSESSMENT OF SUBAXIAL FUSION

> 2 mm movement between spinous processes on dynamic (flexion-extension) cervical spine x-rays is recommended as a criteria for pseudarthrosis (**Level B** Class II), this measurement is unreliable when performed by the treating surgeon (**Level C** Class II)[274].
Visualization of bone trabeculation across the fusion on static films is a less reliable marker for fusion (**Level D** Class III) (2D reformatted CT increases the accuracy (**Level D** Class III))[274]

Pseudarthrosis may occur with or without supplemental anterior cervical plating.

Incidence: Difficult to assess because of lack of validated criteria. Estimate: 2-20%. Higher with dowel technique (Cloward) than with keystone technique of Bailey & Badgley or with interbody method of Smith-Robinson (10%) or with non-fusion advocated by Hirsch. One criteria: motion > 2 mm between the tips of the spinous processes on lateral flexion/extension x-rays[275, 276]. Other criteria: lucencies around the screws of an anterior plate, toggling of the screws on flexion/extension x-rays.

Presentation: Not uniformly associated with symptoms or problems[275, 277]. Some patients may have chronic or recurrent neck pain, some may present with radicular symptoms. (NB: when DePalma's data is analyzed with patients reclassified as failures if neck and/or arm symptoms persist, the success rate of surgery is lower with pseudarthrosis[278]).

Management: (Guidelines are shown in *PRACTICE GUIDELINE 18-10*). No treatment is required for <u>asymptomatic</u> pseudarthrosis. Options for symptomatic

patients include re-resection of the bone graft with repeat fusion[279] (some recommend using autologous bone if allograft was used, a plate may be considered if one was not used previously), cervical corpectomy with fusion[279], or posterior cervical fusion.

PRACTICE GUIDELINE 18-10 MANAGEMENT OF ANTERIOR CERVICAL PSEUDARTHROSIS

Revision of *symptomatic** pseudarthrosis should be considered (**Level D** Class III)[280]. Posterior approaches may be associated with higher fusion rates on revision than anterior approaches (**Level D** Class III)[280]

* italics added

CERVICAL DISC ARTHROPLASTY

PRACTICE GUIDELINE 18-11 CERVICAL DISC ARTHROPLASTY

Cervical arthroplasty is a recommended alternative to ACDF in selected patients for control of arm and neck pain (**Level B** Class II)[253]

An alternative to fusion. Uses an artificial disc to preserve motion at the level of the discectomy. Some of the available cervical disc replacement **(CDR)** models are shown in *Table 18-20*[281].

Table 18-20 Artificial cervical discs

Trade name	Manufac-turer	Material	IAR*	Comment
Prestige®	Medtronic	MOM* (chrome cobalt stainless steel)	variable ball in trough	1st FDA approved CDR; lots of MRI artifact
Bryan®	Medtronic	lubricated elastic nucleus sealed in a flexible membrane	variable in center of disc space	
Advent®	Blackstone (Orthofix)	flexible elastomer core		withdrawn from market
ProDisc-C	Synthes	metal-on-polyethylene	posterior part of inferior VB	midline keel inserts into VB; lots of MRI artifact
Cervicore®	Stryker	MOM	inferior VB	
PCM*®	Cervitech	metal-on-polyethylene	gliding motion	contoured to endplates

* Abbreviations: IAR = instantaneous axis of rotation, MOM = metal-on-metal, PCM = Porous-coated Motion

Booking the case - cervical disc arthroplasty

Also see defaults & disclaimers (*page v*).

1. position: supine, some use halter traction with this
2. equipment:
   A. microscope (not used by all surgeons)
   B. C-arm
3. implants: schedule vendor to provide desired artificial disc
4. neuromonitoring: (optional) some surgeons used SSEP/MEP
5. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the front of the neck to remove the degenerated disc and bone spurs, and to place an artificial disc
   B. alternatives: nonsurgical management, surgical fusion (from the front or the back of the neck)
   C. complications: swallowing difficulties are common but usually resolve, hoarseness of the voice (< 4% chance of it being permanent), injury to: food-pipe (esophagus), windpipe (trachea), arteries to the brain (carotid) with stroke, spinal cord with paralysis, nerve root with paralysis, possible seizures with MEPs (if used). The disc may eventually wear out and further surgery may be needed

Post-op orders:

1. no cervical collar (the goal is to preserve motion at the operated level)
2. NSAIDs around the clock for ≈ 2 weeks (this inhibits bone growth which theoretically helps avoid undesirable fusion at the operated level)

POSTERIOR CERVICAL DECOMPRESSION (CERVICAL LAMINECTOMY)

Not necessary for unilateral radiculopathy (use either ACD or keyhole laminotomy). Consists of removal of cervical lamina (laminectomy) and spinous processes in order to convert the spinal canal from a "tube" to a "trough".

Usually reserved for the following conditions:

1. multiple cervical discs or osteophytes (anterior cervical discectomy **(ACD)** is usually used to treat only 2, or possibly 3, levels without) with myelopathy
2. where the anterior pathology is superimposed on cervical stenosis, and the latter is more diffuse and/or more significant (see *Cervical spinal stenosis*, page 485)
3. in professional speakers or singers where the 4% risk of permanent voice change due to recurrent laryngeal nerve injury with ACD may be unacceptable

Booking the case - cervical laminectomy

Also see defaults & disclaimers (*page v*).

1. position: prone, some use pin headholder
2. equipment:
   A. C-arm
   B. high-speed drill
3. implants: cervical lateral mass screws and rods if fusion is being done
4. neuromonitoring: some surgeons used SSEP/MEP
5. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the back of the neck to remove the bone over the compressed spinal cord and nerves and possibly to place screws and rods to fuse the boned together
   B. alternatives: nonsurgical management, surgery from the front of the neck, posterior surgery without fusion, laminoplasty

C. complications: nerve root injury (C5 nerve root is the most common), may not relieve symptoms necessitating further surgery, possible seizures with MEPs. If fusion is not done, risk of progressive bone slippage which would require further surgery

POSTERIOR KEYHOLE LAMINOTOMY

PRACTICE GUIDELINE 18-12 CERVICAL LAMINOFORAMINOTOMY

Cervical laminoforaminotomy is recommended as a surgical treatment option for symptomatic cervical radiculopathy caused by disc herniation or lateral recess narrowing (**Level D** Class III)[282]

AKA “keyhole foraminotomy”. Decompresses only individual nerve roots (but not the spinal cord) by creating a small “keyhole” in the lamina to access the nerve root.

Indications for keyhole approach (as opposed to anterior discectomy):

1. monoradiculopathy with posterolateral <u>soft</u> disc sequestration (small <u>lateral</u> osteophytic spurs may also be addressed)
2. radiculopathy in patients who are professional speakers or singers (*see above*)
3. for lower (e.g. C7, C8 or T1) or upper (e.g. C3 or C4) cervical nerve root compression, especially in a patient with a short thick neck, making an anterior approach more difficult

Booking the case - cervical keyhole laminectomy

BOOKING

Also see defaults & disclaimers (*page v*).

1. position: prone, some use pin headholder
2. equipment:
   A. microscope (not used by all surgeons)
   B. C-arm
3. instrumentation: some surgeons use a tube retractor system
4. neuromonitoring: some surgeons used SSEP/MEP
5. consent (in lay terms for the patient - not all-inclusive):

A. procedure: surgery through the back of the neck to remove the bone over the compressed nerve root and possibly remove fragment of herniated disc

B. alternatives: nonsurgical management, surgery from the front of the neck, posterior surgery with fusion

C. complications: nerve root injury, may not relieve symptoms necessitating further surgery, possible seizures with MEPs

Technique[283-285]

1. position

   A. prone, on chest rolls. Adhesive tape is used to retract shoulders down for any level below about C4-5. The head is stabilized on a horse-shoe headrest or in a Mayfield head holder.

   B. sitting position: generally abandoned. May be used with proper precautions (*see page 153*)

"Open" keyhole foraminotomy

The desired level is localized with intra-op x-ray or fluoroscopy before making the skin incision, a 2-3 cm midline incision is adequate. A unilateral exposure suffices. Periosteal elevators are used to dissect muscles off the lamina and facet joint in the sub-periosteal plane. A Kocher clamp may be placed on the spinous process to permit confirmation of the correct level on intraoperative x-ray. A Scoville retractor or equivalent is employed.

A high-speed drill (e.g. with diamond burr) is used to make an opening in the medial one-third to one-half of the inferior facet of the vertebra above the desired disc space, extending slightly medially into the junction with the lamina. Once the inferior facet is penetrated, the superior facet of the inferior vertebral level will be visualized. This is also thinned with the drill (it is critical to remove the bone of the superior facet of the level below caudally to where it meets the pedicle). A small Kerrison rongeur may be used to slightly enlarge the laminectomy. An opening is made in the ligamentum flavum overlying the lateral aspect of the spinal cord dura. The nerve root can be identified as it exits from the thecal sac, and can be followed as it travels between the pedicles of the vertebrae above and below. Soft tissues (including ligamentum flavum) form fibrous bands across the dorsum of the nerve, and are removed to further expose the dura of the nerve root. The venous plexus around the nerve root is coagulated with bipolar cautery and then divided to mobilize the nerve. The nerve may then

be gently moved a few millimeters rostrally using a micro nerve hook. The dura overlying the spinal cord should not be manipulated, and the disc space need not be entered. Inspection for free disc fragments should begin in the nerve root axilla using a probe (e.g. blunt nerve hook). Next, the space anterior to the root (the region of the disc) may be palpated. Any disc fragments that are dislodged are removed with a small pituitary rongeur. If the disc fragment is contained anterior to the posterior longitudinal ligament **(PLL)**, the PLL may be incised in the region of the nerve root axilla with a #11 scalpel blade in a motion that is directed downward and laterally, away from the nerve root and spinal cord. The foraminotomy may be extended slightly laterally if the foramen still feels tight when probed. Small osteophytes can potentially be reduced using a small reversed-angled curette, although some surgeons believe that the need for this is obviated by the decompression provided by the keyhole opening. In some cases, simple posterior decompression of the nerve root (without removing a disc fragment) may be adequate to relieve compression. Spinal stability is usually preserved if less than half the facet joint is removed.

MIS keyhole foraminotomy

Positioning as described above.

1. skin incision (use fluoro to locate the correct level for the incision)
    A. incision 1 cm off midline on the side of the pathology at the level of the disc space
    B. remove adhesive plastic barrier (e.g. Ioban®) from around the opening to prevent pieces from being dragged into the incision
2. avoid using a guidewire to reduce the risk of penetrating the interlaminar space. STAY LATERAL and insert the thinnest dilator. Dock the dilator on the lateral mass and insert progressively sized dilators
3. use Bovie to expose lateral lamina and medial facet joint. Start laterally where bone is more easily felt and there is little danger of penetrating the interlaminar space and injuring the spinal cord
4. use a straight curette to expose the inferior edge of the superior lateral lamina and the medial facet joint
5. drill off the medial inferior facet, to expose the superior facet of the level below
6. drill the medial superior facet until you are flush with the superior aspect of the pedicle below
7. this completes the bony work, the soft tissue work proceeds as above

under open keyhole foraminotomy

Outcome

A number of large series have reported good or excellent outcome in the range of 90-96%[284].

18.3.3. Thoracic disc herniation

Key concepts:

> • comprise only 0.25% of herniated discs, and < 4% of operations for herniated disc
> • usually occur at or below T8 (the more mobile portion of the thoracic spine)
> • frequently calcified ∴ get CT through disc (may affect choice of surgical approach)
> • primary indications for surgery: refractory pain, progressive myelopathy
> • surgical treatment: laminectomy is usually not appropriate

Account for 0.25-0.75% of all protruded discs[286]. 80% occur between the 3rd and 5th decades. 75% are below T8 (the more mobile portion of the thoracic spine), with a peak of 26% at T11-12. 94% were centrolateral and 6% were lateral[287]. A history of trauma may be elicited in 25% of cases.

Most common symptoms: pain (60%), sensory changes (23%), motor changes (18%). With thoracic radiculopathy, pain and sensory disturbance is in a band-like distribution radiating anteriorly and inferiorly along the involved root's dermatome. Motor involvement is difficult to document.

SURGICAL TREATMENT

INDICATIONS

Herniated thoracic discs requiring surgery are rare[287]. Indications: refractory pain (usually radicular, bandlike) or progressive myelopathy. Uncommon: symptomatic syringomyelia originating at level of disc herniation.

APPROACHES

Surgery for thoracic disc disease is problematic because of: the difficulty of anterior approaches, the proportionately tighter space between cord and canal

compared to the cervical and lumbar regions, and the watershed blood supply which creates a significant risk of cord injury with attempts to manipulate the cord when trying to work anteriorly to it from a posterior approach. Herniated thoracic discs are calcified in 65% of patients considered for surgery[287] (more difficult to remove from a posterior or lateral approach than non-calcified discs).

Open surgical approaches[287, 288]:

1. posterior (midline laminectomy): primary indication is for decompression of posteriorly situated intracanalicular pathology (e.g. metastatic tumor) especially over multiple levels. There is a high failure and complication rate when used for single-level anterior pathology (e.g. midline disc herniation)
2. posterolateral
   A. lateral gutter: laminectomy plus removal of pedicle.
   B. transpedicular approach[289]
   C. costotransversectomy (*see below*)
   D. transfacet pedicle sparing
3. anterolateral (transthoracic)
4. lateral extracavitary

An option to open surgery is thoracoscopic surgery.

Choice of approach

For anterior approaches to the thoracic spine, see sections beginning on *page 178*.

Intraoperative SSEPs and MEPs may be helpful for cases of myelopathy.

For a laterally herniated thoracic disc without myelopathy: posterolateral approach with medial facetectomy is technically simple, and has generally good results. For a central disc herniation, or when myelopathy is present: transthoracic approach has the lowest incidence of cord injury with the best operative results (*see Table 18-21*). For anterior access, unless pathology is predominantly left-sided, a right-sided thoracotomy is preferred because the heart does not impede access.

Table 18-21 Results with various approaches for thoracic spine pathology[290]

Approach	Indication	Total no.	OUTCOME			
			Normal	Improved	Same	Worse
laminectomy	posteriorly located tumor	129	15%	42%	11%	32%
posterolateral (transpedicular)	radicular pain with lateral disc herniation; biopsy of tumor	27	37%	45%	11%	7%
lateral (costotransversectomy)	fair for midline disc; good ipsilateral access, poor access to opposite side	43	35%	53%	12%	0
transthoracic	best for midline lesions, especially for reaching both sides of cord	12	67%	33%	0	0

COSTOTRANSVERSECTOMY

Indications: in the past this was often used to drain tuberculous spine abscess. It may be used for lateral disc herniation, biopsy of VB or pedicle, limited unilateral decompression of spinal cord from tumor or bone fragments, sympathectomy. Can be used at ≈ any T-spine level. Limitations: difficult to visualize anterior canal to access midline anterior pathology. Better for soft disc than for calcified central disc.

Involves resection of the transverse process and at least ≈ 4-5 cm of the posterior rib. A serious risk of this approach is interruption of a significant radicular artery which may compromise spinal cord blood supply (see *Spinal cord vasculature*, page 95). There is also a risk of pneumothorax which is less grave.

Booking the case - costotransversectomy

BOOKING

Also see defaults & disclaimers (*page v*).

1. position: prone, usually on chest rolls
2. equipment:
   A. microscope (not used for all cases)
   B. C-arm
3. implants: if post-op instability is anticipated, thoracic pedicle screws and possibly a cage (e.g. for fracture or tumor, not typically for disc herniation)
4. neuromonitoring: SSEP/MEP
5. blood availability: type and cross 2 U PRBC
6. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the back of the chest to remove a small

piece of rib to permit removal of the herniated/calcified disc

B. alternatives: nonsurgical management, surgery from the side through the chest

C. complications: spinal cord injury with paralysis, lung complications including pneumothorax or hemothorax (blood or air outside lungs), possible seizures with MEPs

Surgical technique

☞ The approach can be somewhat difficult due to the infrequent encounter with the anatomy by most neurosurgeons. Be prepared for a "deep, red hole, where everything initially looks the same and the bony anatomy is not easy to define". With patience and persistence and the help of an anatomic model in the O.R., the surgeon can get his/her bearings. One of the most helpful landmarks is following the NVB (or just the nerve root) medially to the neural foramen.

In the O.R. before the skin incision, localizing x-rays are obtained; a spinal needle inserted between 2 spinous processes may be used as a marker.

Patient position: the approach is from the side of the pathology/symptoms; for central disc herniations a right-sided approach reduces risk of injury to artery of Adamkiewicz (located on the left in 80%, *see page 96*). Options:

1. lateral oblique, ≈ 30° elevated from straight prone, a "bean-bag" is good for stabilization. For a thin patient, the surgeon may stand in <u>front</u> of the patient (gives more horizontal angle of view - does not work as well with heavier patients due to mass of skin/muscle in the way laterally)
2. prone on chest rolls: the chest roll on the side of the pathology should be more medial to allow the shoulder and scapula to fall forward out of the way

Skin incision: options

1. curved paramedian skin incision: apex oriented away from the midline along the slight depression demarcating the junction of the lateral border of the paraspinal muscles with the ribs (≈ 6-7 cm lateral to midline) centered over the interspace of interest extending ≈ 3 vertebral bodies **(VB)** above and below. The incision is carried through the skin, subcutaneous fat, trapezius, and (for lower 6 thoracic levels, where most thoracic disc herniations occur) the latissimus dorsi, down to the ribs, and this musculocutaneous flap can be reflected medially as a unit
2. midline incision: need to extend 3-4 levels above and below the level of pathology to get an angle low enough to visualize posterior to the facet in

order to access the posterior vertebral body. The inferior aspect can be curved laterally towards the side of pathology. Advantage: a laminectomy can more easily be performed if needed (if the angle does not provide adequate visualization, as a "bail-out" contingency, a facetectomy may be performed, and pedicle may even be removed to access inferior to the disc space. This usually permits easy decompression of the entire thecal sac. In the thoracic spine, stabilization is optional, and if chosen, unilateral pedicle screws and fusion are usually adequate)

Rib removal and thoracic exposure: for a simple biopsy or drainage of a small abscess, removal of only 1 rib may suffice. The rib to be removed is from the level inferior to the disc space to be accessed[291] (e.g. remove the T4 rib to access T3-4). For most other pathologies, 2 or 3 ribs are often removed[292]. To access a VB, the like-numbered rib and the rib below are removed.

There are a number of ligaments attached to the rib: the intercostal neurovascular bundle **(NVB)** courses medial to the superior costotransverse ligament which extends from the superior aspect of the rib to the transverse process of the level above. This ligament and the lateral costotransverse ligament are divided and the transverse process is rongeured off (the base of which lies on the lamina directly posterior to the pedicle). This exposes the rib anterior to the transverse process. The periosteum is incised on the rib from the angle of the rib to the costovertebral articulation, and by subperiosteal dissection around its circumference the pleura is dissected off the anterior surface of the rib. The NVB is dissected from the deep-inferior surface along with the periosteum. The rib is then transected laterally at the angle (≈ 5 cm lateral to the rib head) with rib shears, it is gripped with a clamp, and is rotated while the ligaments (including the radiate ligaments which attach the rib to the both the VB above and the VB below the disc space at the superior and inferior costal facet, respectively, except T1, 11 & 12 which only articulate with their like-numbered VB) are sharply dissected off the rib which is then removed. The removed rib material may be used for fusion substrate except in cases of tumor or infection. The pleura is then dissected from the deep surface of the adjacent ribs and VB (taking care not to injure the segmental vessels and to dissect the sympathetic trunk off the VB with the pleura). The pleura is then retracted laterally with a malleable ribbon or Deaver retractor.

The intervertebral foramen of interest may be located by following the NVB of the rib above proximally, the intercostal nerve (the ventral ramus of the nerve root at that level) enters between the two pedicles. The dura may then be exposed by enlarging the neural foramen by removing part of the pedicles with a

high-speed drill and Kerrison rongeurs.

Instrumentation/fusion are rarely required for simple discectomy. Instability due to fracture, tumor, or extensive resection (e.g. with total facet takedown) necessitates surgical stabilization, typically with pedicle screws/rods extending 2 levels above and 2 levels below. Prior to closure, check for air leak by filling the opening with saline and having the anesthesiologist apply a valsalva maneuver. If an air leak is identified, a Cook catheter may be placed into the pleural space through the surgical exposure, or alternatively a chest tube is placed through a separate intercostal incision after the laminectomy wound is closed. A post-op CXR is obtained regardless of whether an air leak is identified.

TRANSPEDICULAR APPROACH

Drilling down the pedicle and removing a small amount of bone from the vertebral body, then pushing material from the epidural space into the defect created and removing it. Requires removal of just the rib head. Advantages: minimal risk of pneumothorax, more familiar anatomy. Disadvantages: requires instrumentation especially if done bilaterally, the angle is not very obliques so visualization of epidural space is minimal, may need to be done bilaterally if there are extensive bilateral components to the pathology.

Booking the case - transpedicular approach

Same as for costotransversectomy (*see page 472*).

TRANSTHORACIC APPROACH

Indications: thoracic disc disease, burst fractures of the thoracic spine, etc.

Advantages[293]:

- excellent anterior exposure (especially advantageous for multiple levels)
- little compromise of stability (due to supporting effect of rib cage)
- low risk of mechanical cord injury

Disadvantages:

- requires thoracic surgeon (or familiarity with thoracic surgery)
- some risk of vascular cord injury (due to sacrifice of intercostal arteries)
- definitive diagnosis may not be possible if it is uncertain prior to procedure

Possible complications:

• pulmonary complications: pleural effusion, atelectasis, pneumonia, empyema, hypoventilation
• CSF-pleural fistula

Booking the case - transthoracic spine surgery

Also see defaults & disclaimers (*page v*).

1. position: typically on the side, often on a beanbag
2. equipment:
   A. microscope (not used for all cases)
   B. C-arm
3. anesthesia: double lumen tube
4. implants: if post-op instability is anticipated, thoracic pedicle screws and possibly a cage (e.g. for fracture or tumor, not typically for disc herniation)
5. neuromonitoring: SSEP/MEP
6. blood availability: type and cross 2 U PRBC
7. some surgeons use chest surgeon for the approach, closure and for follow-up
8. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the chest with removal of a small piece of rib to permit removal of the herniated/calcified disc
   B. alternatives: nonsurgical management, surgery from the side or through the back
   C. complications: spinal cord injury with paralysis, pneumothorax, possible seizures with MEPs

Key technical points

1. the services of an experienced thoracic surgeon are usually engaged
2. position: true lateral (facilitates intra-op localizing x-rays); approached from the more involved side. For the upper thoracic midline region, some prefer right-side-up to eliminate thoracic aorta from obstructing exposure and to reduce the possibility of encountering the artery of Adamkiewicz[294], others prefer left-side-up to use the aorta as a landmark[293] (for levels below the cardiophrenic angle, a left-sided

approach is preferred because the inferior vena cava is difficult to mobilize)

3. usually one rib is resected; most often the rib of the vertebra immediately above the disc space desired (facilitates exposure). Multiple ribs may be resected to increase exposure
4. when removing the vertebral body **(VB)** (corpectomy, e.g. for osteomyelitis, especially Pott's disease or for kyphoscoliosis)
   A. the posterior cortex of the VB must be pulled anteriorly (e.g. with angled curettes) to avoid mechanical cord trauma
   B. anterior fusion may be performed using the removed rib. If inadequate, fibula or iliac crest may be used
5. sizeable radicular arteries are spared. The intercostal nerve is used as a guide to the intervertebral foramen (nerve enters foramen superiorly and posteriorly)
6. the disc space is situated off the caudal aspect of the intervertebral foramen for most thoracic levels
7. one or two intervertebral arteries and veins usually have to be sacrificed; to minimize the risk of ischemic cord injury, cut them as close to the midline of the spine as possible (collaterals tend to lie on the lateral aspect of the spine)
8. the sympathetic chain is dissected off the VBs and is pushed posteriorly

Lateral approach

The same instrumentation used for lateral lumbar interbody fusion (*see page 194*) may be used to access the lateral thoracic bodies for thoracic disc herniation.

Check the pre-op MRI for the location of the aorta and to rule-out aortic aneurysm. Above T11, enter on the right side. The access retractor is "reversed" so that the center blade is positioned anteriorly and the shim is place so that as the retractor is expanded in the AP direction, the lateral blades move posteriorly, giving more access to the posterior disc space. In general, do not penetrate the contralateral anulus because of proximity of aorta. At or just below L12-L1, the diaphragm attached to the VB. A dual lumen endotracheal tube is not required. A chest tube is mandatory if there is an air leak, otherwise it is optional (a pigtail catheter may suffice).

18.4. Degenerative disc/spine disease

Since structures outside of the disc are usually also involved, the term degenerative spine disease **(DSD)** may be preferable to degenerative *disc* disease. Spondylosis is a non-specific term which may include degenerative spine disease. “Cervical spondylosis” is occasionally used synonymously with cervical stenosis (see *Cervical spinal stenosis*, page 485).

DSD is a progressive deterioration of the structures of the spine including:

1. disc abnormalities:
   A. the proteoglycan content of the disc nucleus decreases with age
   B. disc desiccation (loss of hydration) occurs
   C. tears develop in the disc annulus and progress to internal disruption of the lamellar architecture. Herniation of the nucleus may occur from increased nuclear pressure under mechanical loads
   D. mucoid degeneration and ingrowth of fibrous tissue ensues (disc fibrosis)
   E. subsequently disc resorption occurs
   F. there is a loss of disc space height and increased susceptibility to injury
2. facet joint abnormalities: hypertrophy and capsular laxity
3. osteophytes often form on the edges of the VB bordering the degenerated disc
4. spondylolisthesis: subluxation of one VB on another (see *Spondylolisthesis* below)
5. spondylolysis: alternative term for isthmic spondylolisthesis (*see below*), a failure of the neural arch due to a defect in the pars interarticularis which may present as spondylolisthesis. There may be a fibrous mass from the nonunion
6. hypertrophy of the ligamentum flavum

Clinical presentation:

1. the above abnormalities may produce **spinal stenosis** which can lead to neural compromise producing the following symptoms
   A. radicular symptoms (more common in cervical spine than lumbar)
   B. neurogenic claudication (lumbar) or spinal myelopathy (cervical)
2. discogenic pain (controversial) may be less prevalent in the late stages of DSD. May contribute to “musculoskeletal low back pain” but the actual pain generators here are not definitively identified

Etiology

The etiology of DSD is multifactorial and includes:

1. cumulative effects of microtrauma and macrotrauma to the spine
2. osteoporosis
3. cigarette smoking: several epidemiologic studies have shown that the incidence of back pain, sciatica and spinal degenerative disease is higher among cigarette smokers than among nonsmokers[295, 296]
4. in the lumbar spine:
   A. stresses on the spine including effects of excess body weight
   B. loss of muscle tone (primarily abdominals and paraspinals) resulting in increased dependence on the bony spine for structural support

SPONDYLOLISTHESIS

Anterior subluxation of one vertebral body on another. Usually L5 on S1, the next most common is L4 on L5. The Meyerding[297, 298] grading of subluxation in the sagittal plane is shown in *Table 18-22*.

Disc herniation and nerve root compression: It is rare for a herniated lumbar disc to occur at the level of the listhesis, however the disc may "roll" out as it is exposed and produce findings on MRI that have been termed a "pseudodisc". It is more common to see a herniated disc at the level above the listhesis. If the listhesis does cause nerve root compression, it tends to involve the nerve exiting below the pedicle of the anteriorly subluxed vertebra. The compression is usually due to upward displacement of the superior articular facet of the level below together with disc material, and symptoms typically resemble neurogenic claudication, although true radiculopathy may sometimes occur.

Table 18-22 Spondylolisthesis grading

Grade	% subluxation*
I	< 25%
II	25-50%
III	50-75%
IV	75%-complete
spondyloptosis	> 100%

* % of the AP diameter of the VB

Classification of Spondylolisthesis

Type 1: dysplastic: congenital. Upper sacrum or arch of L5 permits the spondylolisthesis. No pars defect. 94% are associated with spinal bifida occulta. Some of these may progress (no way to identify these)

Type 2: isthmic spondylolisthesis AKA **spondylolysis**: a failure of the neural arch manifesting as a defect in the **pars interarticularis** (the neck of the "Scotty dog" on oblique LS-spine x-ray). May be seen in 5-20% of spine x-rays[4]. Three subtypes:

C. lytic: fatigue fracture or insufficiency fracture of pars. In the pediatric age group may occur in athletes (especially gymnasts or football players); in some this may be an exacerbation of a pre-existing defect, in others it may be a result of repetitive trauma

D. elongated but intact pars: possibly due to repetitive fractures and healing

E. acute fracture of pars Type 3: degenerative: due to long-standing intersegmental instability. Usually at

L4-5. No break in the pars. Found in 5.8% of men and 9.1% of women (many of whom are asymptomatic)[4]

Type 4: traumatic: due to fractures usually in areas other than the pars

Type 5: pathologic: generalized or local bone disease, e.g. osteogenesis imperfecta

ISTHMIC SPONDYLOLISTHESIS (SPONDYLOLYSIS) - PARS INTERARTICULARIS DEFECT

Presentation

Isthmic spondylolisthesis rarely produces central canal stenosis since only the anterior part of the spinal canal is shifted forward. May present with radiculopathy, with the nerve exiting under the pedicle at that level being the most vulnerable. May also present with low back. Many cases are asymptomatic.

Management[4]

1. lesions with sclerotic borders are usually well established with little chance of healing. Surgery is reserved for patients with neurologic deficit or incapacitating symptoms
2. lesions without sclerosis that show increased uptake on bone scan (indicating active lesion with potential for healing) or MRI high signal changes on T2WI[299] or

STIR may heal in a rigid orthosis such as the **Boston brace** for ≥ 3 months
3. management of symptoms:
   A. LBP only: treat with NSAIDs, PT
   B. LBP with myelopathy, radiculopathy, or neurogenic claudication: surgical treatment[300] (*see Table 18-23* for surgical options)
4. in pediatrics: may be managed with TLSO and long course of PT (e.g. 6-9 months) for symptoms. Resumption of sports may be considered when symptoms subside, but recurrence should prompt elimination of athletics or consideration of surgery

SURGICAL CONSIDERATIONS

When surgery is indicated, *Table 18-23* serves as a guide to the type of procedure.

Table 18-23 Surgical recommendations for spondylolisthesis

Nature of spondylolisthesis	Nature of problem	Type of procedure needed
degenerative	nerve root compression within confines of spinal canal	decompression (preserving facets)
	spinal stenosis at the level of spondylolisthesis	decompression; some advocate with intertransverse-process fusion[301]
	nerve root compression far lateral, outside confines of spinal canal	radical decompression (Gill procedure, *see below*) plus fusion
traumatic	(does not matter)	decompression plus fusion

Reduction of high-grade (grade III or IV) spondylolisthesis carries a risk of radiculopathy (e.g. L5 radiculopathy in cases of L5-S1 spondylolisthesis) in 50% of cases (some permanent) and may produce a cauda equina syndrome, probably from stretching nerve roots by distraction. The risk of nerve root injury with reduction of grade I or II spondylolisthesis is low.

Gill procedure: This procedure, and its modifications[302], consist of radical decompression of nerve roots including removal of the loose posterior elements and total facetectomy. This is often followed by fusion (posterolateral or interbody). Fusion rate may be enhanced with the use of internal fixation (e.g. transpedicular screw-rod fixation)[303].

18.4.1. Spinal stenosis

Classified as:

1. central canal stenosis: narrowing of the AP dimension of the spinal canal. The reduction in canal size may cause local neural compression and/or compromise of the blood supply to the spinal cord (cervical) or the cauda equina (lumbar)
2. foraminal stenosis: narrowing of the neural foramen. May be the result of any combination of: foraminal disc protrusion, spondylolisthesis, facet hypertrophy, disc space collapse, hypertrophy of uncovertebral joints (cervical), synovial cyst
3. lateral recess stenosis (lumbar spine only): *see page 484*

Central canal stenosis

May be congenital (as in the achondroplastic dwarf), acquired, or most commonly acquired superimposed on congenital.

In the lumbar region, the syndrome of neurogenic claudication (*see below*) is well recognized. In the cervical region, cervical myelopathy and ataxia (from spinocerebellar tract compression) may be present. In 5%, lumbar and cervical stenoses are symptomatic simultaneously[304]. Symptomatic spinal stenosis in the thoracic region is rare[305].

18.4.1.1. Lumbar spinal stenosis

Unless indicated otherwise, this discussion refers primarily to central canal stenosis

Key concepts:

- caused by hypertrophy of facets and ligamentum flavum, may be exacerbated by disc bulging or spondylolisthesis, may be superimposed on congenital narrowing
- most common at L4-5 and then at L3-4
- symptomatic stenosis produces gradually progressive back and leg pain with standing and walking that is relieved by sitting or lying (neurogenic claudication)
- symptoms differentiated from vascular claudication which is usually relieved at rest regardless of position
- usually responds to decompressive surgery (sometimes with fusion) or interspinous spacer

Symptomatic lumbar stenosis is most common at L4-5, then L3-4, L2-3 and lastly L5-S1306. It is rare at L1-2. Generally occurs in patients with congenitally shallow lumbar canal (see *Normal LS spine measurements*, page 480) with superimposed acquired degeneration in the form of some combination of facet hypertrophy, hypertrophy of the ligamentum flavum, protruding (and often calcified) intervertebral discs, and spondylolisthesis. First recognized as a distinct clinical entity producing characteristic symptoms in the 1950's and 60's[307, 308].

May be classified as[309]:

1. **stable** form of lumbar spinal stenosis: hypertrophy of facets and ligamentum flavum accompanied by disc degeneration and collapse
2. **unstable**: have the above with superimposed
   A. degenerative spondylolisthesis: (*see page 475*) the unisegmental form
   B. degenerative scoliosis: the multisegmental form

CLINICAL EVALUATION

PRESENTATION

Often presents as **neurogenic claudication (NC)**, (claudicate: from Latin, *claudico*, to limp) AKA **pseudoclaudication**. To be differentiated from **vascular claudication** (AKA intermittent claudication) which results from ischemia of exercising muscles (*see Table 18-24*). NC characteristics: unilateral or bilateral buttock, hip, thigh or leg discomfort that is precipitated by standing or walking and characteristically relieved by a change in posture.

NC is thought to arise from ischemia of lumbosacral nerve roots, as a result of increased metabolic demand from exercise together with vascular compromise of the nerve root due to pressure from surrounding structures. NC is only moderately sensitive (≈ 60%) but is highly specific for spinal stenosis[311]. Pain may not be the major complaint, instead, some patients may develop paresthesias or LE weakness with walking. Some may complain of muscle cramping, especially in the calves.

Relief from symptoms: occurs with positions that decrease the lumbar lordosis which increases the diameter of the central canal (by reducing inward buckling of the ligamentum flavum) and distracts the facet joints (which enlarges the neural foramina. Favored positions include sitting, squatting and recumbency. Patients may develop "**anthropoid posture**" (exaggerated waist flexion). "Shopping cart sign" patients often can walk farther if they can lean

forward e.g. as on a grocery cart. Riding a bicycle is also often well tolerated.

Table 18-24 Clinical features distinguishing neurogenic from vascular claudication[310]

Feature	Neurogenic claudication	Vascular claudication
distribution of pain	in distribution of nerve (dermatomal)	in distribution of muscle group with common vascular supply (sclerotomal)
sensory loss	dermatomal distribution	stocking distribution
inciting factors	variable amounts of exercise, also with pro-longed maintenance of a given posture (65% have pain on standing at rest); coughing produces pain in 38%	reliably reproduced with fixed amount of exercise (e.g. distance ambulated) that decreases as disease progresses; rare at rest (27% have pain on standing at rest)
relief with rest	slow (often > 30 min), variable, usually positional (stooped posture or sitting often required, ★ <u>standing and resting is usually not sufficient</u>)	almost immediate; not dependent on posture (relief of walking induced symptoms with standing is a key differentiating feature)
claudicating distance	variable day-to-day in 62%	constant day-to-day in 88%
discomfort on lifting or bending	common (67%)	infrequent (15%)
foot pallor on elevation	none	marked
peripheral pulses	normal; or if ↓ usually reduced only unilaterally	↓ or absent; femoral bruits are common
skin temp of feet	normal	decreased

Neurologic exam

The neurologic exam is normal in ≈ 18% of cases (including normal muscle stretch reflexes and negative straight leg raising). Absent or reduced ankle jerks and diminished knee jerks is common[311]. Pain may be reproduced by lumbar <u>extension</u>.

Differential diagnosis

1. vascular insufficiency: (AKA vascular or intermittent claudication) *see above*
2. hip disease: trochanteric bursitis (*see below*), degenerative joint disease
3. disc herniation (lumbar or thoracic)
4. facet joint pain (controversial): may respond to medial branch block (therapeutic & diagnostic)

5. **Baastrup's syndrome**[312]: AKA arthrosis interspinosa. Radiographically: contact of adjacent spinous processes ("kissing spines") with enlargement, flattening and reactive sclerosis of apposing interspinous surfaces. Produces localized midline lumbar pain & tenderness on back extension relieved by flexion, local anesthetic injection or partial excision of the involved spinous processes
6. juxtafacet cyst: *see page 456*
7. arachnoiditis
8. intraspinal tumor
9. Type I spinal AVM (spinal dural AVM): *see page 507*
10. diabetic neuritis: with this, the sole of the foot is usually very tender to pressure from the examiner's thumb
11. delayed onset muscle soreness (DOMS): onset usually 12-48 hours after beginning a new activity or changing activities (NC occurs *during* the activity). Symptoms typically peak within 2 days and subside over several days
12. inguinal hernia: typically produces groin pain
13. functional etiologies

Trochanteric bursitis (TBS) and degenerative arthritis of the hip are also included in the differential diagnosis of NC[313, 314]. Although TBS may be primary, it can also be secondary to other conditions including lumbar stenosis, degenerative arthritis of the lumbar spine or knee, and leg length discrepancy. TBS produces intermittent aching pain over the lateral aspect of the hip. Although usually chronic, it occasionally may have acute or subacute onset. Pain radiates to lateral aspect of thigh in 20-40% (so called "**pseudoradiculopathy**"), but rarely extends to the posterior thigh or as far distally as the knee. There may be numbness and paresthesia-like symptoms in the upper thigh which are usually not dermatomal in distribution. Like NC, the pain may be triggered by prolonged standing, walking and climbing, but unlike NC it is also painful to lie on the affected side. Localized tenderness over the greater trochanter can be elicited in virtually all patients, with maximal tenderness at the junction of the upper thigh and greater tro-chanter. Pain increases with weight bearing (and is often present from the very first step, unlike NC) and with certain hip movements, especially external rotation (over half the patients have a positive Patrick-FABERE test, *see page 444*), and rarely with hip flexion/extension. Treatment includes NSAIDs, local injection of glucocorticoid (usually with local anesthetic), physical therapy (with stretching and muscle strengthening exercises) and local application of ice.

No controlled studies have compared these.

ASSOCIATED CONDITIONS

1. congenital:
   A. achondroplasia
   B. congenitally narrowed canal
2. acquired:
   A. spondylolisthesis
   B. acromegaly
   C. post-traumatic
   D. Paget's disease (see *Paget's disease*, page 498)
   E. ankylosing spondylitis: *see page 502*
   F. ossification of the ligamentum flavum: more common in East Asians, rare in Caucasians[315]. Often, but not always, associated with OPLL[316]

DIAGNOSTIC EVALUATION

RADIOGRAPHIC EVALUATION

Comparison of modalities:

Lumbosacral spine x-rays: may disclose spondylolisthesis. AP diameter of canal is usually narrowed (congenitally or acquired) (see *Normal LS spine measurements* below) whereas the interpediculate distance **(IPD)** may be normal[310]. Oblique films may demonstrate pars defects.

CT scan (either routine, or following water-soluble myelography): classically shows "**trefoil**" canal (cloverleaf shaped, with 3 leaflets). CT also demonstrates AP canal diameter, hypertrophied ligaments, facet arthropathy, and bulging annulus or herniated disc. CT is poor for demonstrating spondylolisthesis although the pars defect may be seen.

Myelogram: lateral films often show "washboard pattern" (multiple anterior defects), AP films often show "wasp-waisting" (narrowing of dye column), may also show partial or complete (especially in prone position) block. May be difficult to perform LP if stenosis is severe (poor CSF flow and difficulty avoiding nerve roots).

MRI: demonstrates impingement on neural structures and loss of CSF signal on T2WI at severely stenotic levels. MRI is poor for visualizing bone which contributes significantly to the pathology (may be helpful for surgical planning). Good for evaluating nerve impingement due to spondylolisthesis (possibly better

than myelogram/CT) and juxtafacet cysts. Asymptomatic abnormalities are demonstrated in up to 33% of asymptomatic patients 50-70 years old[306].

Table 18-25 Normal AP diameter on lateral plain film

(from spinolaminar line to posterior vertebral body)[317]

average (normal)	22-25 mm
lower limits of normal	15 mm
severe lumbar stenosis	< 11 mm

Table 18-26 Normal measurements on CT[318]

AP diameter	≥ 11.5 mm
interpediculate distance (IPD)	≥ 16 mm
canal cross-sectional area	≥ 1.45 cm^2
ligamentum flavum thickness[319]	≤ 4-5 mm
height of lateral recess (*see below*)	≥ 3 mm

Normal LS spine measurements

Normal dimensions of the lumbar spine are shown in *Table 18-25* for plain film and *Table 18-26* for CT.

Interpediculate distance (IPD): The transverse diameter of the spinal canal. On plain AP x-ray of lumbar spine, an IPD < 25 mm suggests stenosis. Average normal IPDs in the lumbar and lower thoracic spine appears in *Table 18-27*. An approximation for the lumbar spine is given in *Eq 18-1*.

$$\boxed{\text{IPD (mm)} = (\text{lumbar level} + 12) \times 1.5} \qquad \textbf{Eq 18-1}$$

Adjuncts to radiographic evaluation

"Bicycle test": patients with NC can usually tolerate longer periods of exercise on a bicycle than patients with intermittent (vascular) claudication because the position in bicycling flexes the waist.

Ratio of ankle to brachial blood pressure **(A:B ratio)**: > 1.0 is normal; mean of 0.59 in patients with intermittent claudication; 0.26 in patients with rest pain; < 0.05 indicates impending gangrene.

Vascular lab studies (e.g. Doppler) may assist in identifying vascular insufficiency.

EMG with NCV may show multiple nerve-root abnormalities bilaterally.

Table 18-27 Normal interpediculate distance (IPD) on AP LS film[320]

Level	IPD (mm)*
T10	16-22
T11	17-24
T12	19-27
L1	21-29
L2	21-30
L3	21-31
L4	21-33
L5	23-37

TREATMENT

In one study of 27 unoperated patients, 19 remain unchanged, 4 improved, and 4 worsened (mean follow-up: 49 months; range: 10-103 months)[321]. NSAIDs (recent evidence suggests acetaminophen may be as effective) and physical therapy are the mainstays of nonsurgical management.

Surgical decompression is undertaken when symptoms become severe in spite of medical management. The goals of surgery are pain relief, halting progression of symptoms, and possibly reversal of some existing neurologic deficit. Most authors do not consider surgery unless the symptoms have been present > 3 months, and most patients who have surgery for this have symptoms of > 1 year duration.

SURGERY

Surgical options

1. laminectomy: posterior (direct) decompression of central canal and neural foramina without or with fusion. Fusion options:
   A. posterolateral fusion ± pedicle screw/rod fixation
   B. interbody fusion: generally not done as a “stand-alone” (i.e. usually requires additional stabilization, options here include: pedicle screws, facet screws, facet dowels, spinous process clamp…)
      1. posterior lumbar interbody fusion (PLIF): usually bilateral graft placement (*see page 193*)
      2. transforaminal lumbar interbody fusion (TLIF): unilateral graft

placement though a facet take-down on that side (*see page 193*)

2. procedures to increase disc space height and thereby <u>indirectly</u> decompress neural foramina without direct decompression
   A. anterior lumbar interbody fusion (ALIF): through laparotomy (*see page 195*)
   B. lateral lumbar interbody fusion: some techniques trademarked as extreme lateral interbody fusion (XLIF™) or direct-lateral (DLIF™): *see page 194*
   C. axial lumbar interbody fusion (Ax-LIF): L5-S1 only (*see page 195*)
3. limitation of extension by interspinous spacer: e.g. X-Stop® (*see below*)

BOOKING THE CASE - LUMBAR LAMI ± FUSION FOR STENOSIS

Also see defaults & disclaimers (*page v*).

1. position: prone
2. implants: for fusions, schedule with the vendor for the desired implants and associated instrumentation
3. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: through the back to remove bone, ligament and any other tissue that is pressing on the nerve(s). If a fusion is to be done, then typically this will be accomplished using screws, rods and small cages, as required
   B. alternatives: nonsurgical management
   C. complications: (usual spine surgery complications - *see page v*) *plus* there might not be the amount of pain relief desired (back pain does not respond as well to surgery as nerve-root pain). If implants are used, then there can be problems with them including breakage, migration (slippage), or undesirable positioning which may require further surgery

Choosing which procedure to use

Although beyond the scope of this book, items that factor into consideration when choosing which procedure to use include:

1. consider indirect decompression (lateral interbody fusion (e.g. XLIF® or DLIF®), interspinous decompression (e.g. X-Stop):
   A. when foraminal stenosis appears to be the dominant problem (e.g.

with loss of disc space height, facet hypertrophy, on the concave side of a scoliotic curve)
  - B. previous spine surgery that might make exposure of the nerves more difficult or risky
2. consider direct decompression (e.g. laminectomy)
  - A. “pinpoint” central canal stenosis especially when disc height and neural foramina are well preserved
  - B. where the majority of the compression is due to a focal, correctable lesion, such as a herniated disc, synovial cyst, intraspinal tumor
3. consider motion-preservation surgery
  - A. when a fusion is undertaken at a level and the adjacent level is already starting to show some degenerative changes that have not yet reached a surgical magnitude. Motion preservation at this adjacent segment theoretically shield it from some of the transmitted stresses from the fused level
4. situations where a fusion should be considered in addition to direct or indirect decompression of the nerves:
  - A. spondylolisthesis (especially > Grade I)
  - B. dynamic instability on flexion/extension lateral lumbar spine x-rays
  - C. expectation that the decompression will destabilize the spine (e.g. facet takedown for a TLIF)
  - D. multiply recurrent herniated disc (when this is the third or more operation for the same disc
  - E. controversial situations:
    1. e.g. a “black disc” on MRI with positive concordant discogram at this level: fusion without decompression has been advocated when there is no neural compression

Laminectomy/laminotomy - surgical technique

Posterior approach with removal of the spines and lamina of affected levels (surgical “unroofing”), along with the associated ligamentum flavum. Individual nerve roots are palpated for compression within their neural foramen, with foraminotomies performed at appropriate levels. Doing a total L4 laminectomy for stenosis allows access to the L4-5 foramen, and the upper part of the L5-S1 foramen. If, in addition, the lower part of L3 is also removed, access is gained to the inferior pedicle of L3 and thus the L3-4 neural foramen. Undercutting the superior articular facet is often necessary to decompress the nerves in the

foramen (see *Lateral recess syndrome*, page 484). Treatment of moderate stenosis at adjacent levels appears warranted as these levels have been shown to have a significant likelihood of becoming symptomatic later[221].

Alternatively, laminotomies (as opposed to laminectomies) may be performed in cases where the central canal has a normal AP diameter, but the lateral canal gutter is stenotic[322, 323]. Multilevel subarticular fenestrations are another slight variation on this theme[324].

Position: either of the following is acceptable

1. prone: on a frame or chest rolls or knee-chest position to decompress the abdomen to decrease venous pressure and thus reduce bleeding
2. lateral decubitus position: if there is no laterality to symptoms, right lateral decubitus (left-side-up) is easier for most right-handed surgeons to use angled Kerrison rongeur parallel to nerve roots

Minimally invasive spine surgery (MISS) decompression

Usually a "mini-open" technique using ≈ 1" incisions and expandable retractors.

1. options include bilateral laminotomies (*see above*)
2. bilateral decompression through a unilateral laminotomy
   A. entry site: 3.5-4 cm off the midline to permit the needed angle
   B. when using a retractor with an "open side" orient the retractor with the open side facing laterally (e.g. with the Nuvasive Maxcess® place the handles medially) to permit the angle needed for contralateral decompression
   C. the laminectomy and facet takedown (usually for a TLIF) are done
   D. open the ligamentum flavum on the side you're working on, to visualize the posterior extent of the spinal canal, to permit finding the plane between the posterior part of the ligamentum flavum and the undersurface of the bone
   E. the ligamentum flavum is left in place on the contralateral side to protect the dura during drilling
   F. complete the decompression and disc removal on the side you're working on
   G. the undersurface of the bone (spinous process and contralateral lamina) are then drilled to decompress the contralateral side
   H. once the undersurface of the contralateral posterior canal has been

drilled, the ligamentum flavum is removed with pituitary rongeurs. It is possible to even do a contralateral foraminotomy at this point (curved Kerrison rongeurs are very helpful for this)

I. pedicle screws are placed through the open side, and then percutaneously through the contralateral side

Interspinous process decompression/stabilization/fusion

Interspinous spacers (e.g. X-Stop™ (Medtronic)) limit extension at 1 or 2 levels (without fusion), preventing narrowing of the associated neural foramen, and may also off-load the facet joints and even the disc. “Success rate”: 63% at 2 years. This device may be used as a standalone.

Interspinous plates (e.g. Aspen® (Lanx), Affix™ (Nuvasive), Spire® (Medtronic)) clamp across two spinous processes to fixate them (unlike X-Stop™ which just limits extension). The Aspen® clamps have a space for a graft which may optionally be used to promote fusion between the spinous processes. Interspinous plates may be used to augment other constructs e.g. lateral interbody fusion[325], but are <u>not</u> intended for standalone use. Biomechanical stability is reported to be similar to bilateral pedicle screws in flexion, and unilateral pedicle screws in lateral bending[326].

Contraindications (includes exclusionary criteria from the IDE study):

1. instability at level considered for procedure: spondylolisthesis > Grade 1 or scoliosis with Cobb angle ≥ 25° (*see page 430*)
2. cauda equina syndrome
3. acute fracture of the spinous process
4. bilateral pars defects (disconnects spinous process from the anterior elements)
5. osteoporosis. Contraindications per the IDE: DEXA scan (*see page 992*) with spine or hip T-score < –2.5 (i.e. more than 2.5 SD below the mean for normal adults) in the presence of ≥ 1 fragility fractures. Concerns: spinous process fracture at the time of insertion, or late subsidence due to microfractures. However, Kondrashov[327] interprets a T-score < –2.5 anywhere as indicative of osteoporosis (even without fragility fractures). Options here include:
   A. augmenting the spinous processes by injecting ≈ 0.5-1 cc of PMMA into each spinous process **(SP)** with a 13 Ga needle inserted ≈ halfway

into the SP on lateral fluoro[327] prior to dilating the interspace or placing the X-Stop. Verify central position within SP on AP fluoro, and monitor injection on fluoro

B. use of an X-Stop made of PEEK (modulus of elasticity of PEEK is closer to bone than titanium) - available now in Europe, soon in the U.S.

6. ankylosed level (i.e. already fused)
7. L5-S1 level: the spinous process of S1 is usually too small (not usually an issue since symptomatic stenosis at L5-S1 is rare)
8. age < 50 years: not studied in IDE investigation

Surgical pointers:

1. it is critical that the spacer sit in the anterior third of the spinous process
2. results may be better with the patient awake, under local anesthesia, lying on their side in a position that they feel is relieving their pain (thus opening up the critical levels). This may reduce the risk of undersizing the prosthesis

Post-op (based on manufacturer's recommendations):

1. to avoid spinous process stress fracture: build-up physical activity gradually
2. 1st 6 weeks post-op: no spine hyperextension, no heavy lifting. Minimize stair climbing
3. initially, walking (for < 1 hour) is recommended as long as it is comfortable
4. at 2 weeks post-op: cycling (stationary or bicycle) may be added
5. 6 months post-op: may add sports such as swimming, golf, racquetball, tennis, running or jogging

Progression of spondylolisthesis

May occur without decompression, but is more common following surgery[328]. However, lumbar instability following decompressive laminectomy is rare (only ≈ 1% of all laminectomies for stenosis will develop progressive subluxation). Fusion is rarely required to prevent progression of subluxation with degenerative stenosis[329].

Stability (without need for instrumentation) is thought to be maintained if > 50-66% of the facets are preserved during surgery and the disc space is not violated (maintains integrity of anterior and middle column). Younger or more

active patients are at higher risk of subluxing.

One approach is to obtain flexion/extension x-rays pre-op, and follow patients after decompression. Those who develop symptomatic slippage post-op are treated by fusion, possibly in conjunction with spinal instrumentation.

Instrumentation and/or fusion

PRACTICE GUIDELINE 18-13 FUSION IN PATIENTS WITH LUMBAR STENOSIS *WITHOUT* SPONDYLOLISTHESIS

Level III[330]:

- in situ posterolateral fusion is not recommended following decompression in patients with lumbar stenosis in whom there is no evidence of preexisting spinal instability or likely iatrogenic instability due to facetectomy
- in situ posterolateral fusion is recommended in patients with lumbar stenosis in whom there is evidence of spinal instability
- the addition of pedicle-screw instrumentation is not recommended in conjunction with posterolateral fusion following decompression

PRACTICE GUIDELINE 18-14 FUSION IN PATIENTS WITH LUMBAR STENOSIS AND SPONDYLOLISTHESIS

Level II[331]: posterolateral fusion is recommended for patients with stenosis and associated degenerative spondylolisthesis who require decompression

Level III[331]: pedicle screw fixation as an adjunct to posterolateral fusion should be considered in patients with stenosis and spondylolisthesis in cases where there is pre-op evidence of spinal instability* or kyphosis* at the level of the spondylolisthesis or when iatrogenic instability is anticipated

* the definition of "instability" and "kyphosis" varies, and has not been standardized

Fusion may accelerate degenerative changes at adjacent levels. Some surgeons recommend fusion at levels of spondylolisthestic stenosis[221, 309]. Patients with combined degenerative spondylolisthesis, stenosis, and radiculopathy may be reasonable candidates for fusion[1].

Brace therapy

PRACTICE GUIDELINE 18-15 BRACE THERAPY AS AN ADJUNCT TO OR INSTEAD OF LUMBAR FUSION
Level II[332]: • short-term use (1-3 weeks) of a rigid lumbar support is recommended for treatment of LBP of relatively short duration (< 6 months) • bracing in patients with LBP > 6 months duration is <u>not</u> recommended because it has not been shown to have long-term benefit

PRACTICE GUIDELINE 18-15 BRACE THERAPY AS AN ADJUNCT TO OR INSTEAD OF LUMBAR FUSION
Level III[332]: • lumbar braces may reduce the number of sick days due to LBP among workers with a previous lumbar injury. Braces are <u>not</u> recommended for LBP in the general working population • the use of pre-op bracing or transpedicular external fixation as tools to predict outcome for lumbar fusion is not recommended

OUTCOME

Morbidity/mortality

Risk of in-hospital mortality is 0.32%[311]. Other risks include: unintended durotomy (*see page 450*) (0.32%[311] to ≈ 13%[329, 333]), deep infection (5.9%), superficial infection (2.3%), and DVT (2.8%) (see also *Risks of lumbar laminectomy* on page 449).

Nonunion

Risk factors for nonunion (does not necessarily correlate with success of operation):

1. cigarette smoking delays bone healing and increases the risk of pseudoarthrosis following spinal fusion procedures, especially in the lumbar spine[295]
2. number of levels: in lumbar fusions, fusing 2 levels resulted in increased non-union rates compared to fusing 1 level[334]
3. NSAIDs: controversial

A. short-term (≤ 5 days) post-op use: high-dose ketorolac (120-240 mg/d) was associated with increased risk of nonunion, but low-dose ketorolac (≤ 110 mg/d), and celecoxib (200–600 mg/d) or rofecoxib (50 mg/d) were not[334]

B. some feel that long-term NSAID use does lower fusion rate[335]

Success of operation

No randomized study exists comparing surgery to "conservative" treatment. Patients with a postural component to their pain had much better results (96% good result) than those without a postural component (50% good results), and the relief of leg pain was much more successful than relief of back pain[336]. Surgery is most likely to reduce LE pain and improve walking tolerance[1].

Surgical failure may be divided into two groups:

1. patients with initial improvement who develop recurrent difficulties. Although short-term improvement after surgery is common, many patients progressively deteriorate over time[337]. One study found a 27% recurrence of symptoms after 5 years follow-up[221] (30% due to restenosis at the operated level, 30% due to stenosis at a new level; 75% of these patients respond to further surgery). Other etiologies include: development of herniated lumbar disc, development of late instability, coexisting medical conditions
2. patients who fail to have any post-op pain relief (early treatment failures). In one series of 45 such patients[338]:
   A. the most common finding was a lack of solid clinical and radiographic indications for surgery (e.g. non-radicular LBP coupled with modest stenosis)
   B. technical factors of surgery had less influence on outcome, with the most common finding being failure to decompress the lateral recess (which requires judicious medial facet resection or undercutting the superior articular facet)
   C. other diagnoses (e.g. arachnoiditis), missed diagnosis (e.g. spinal AVM)

Long term outcome: Literature review[311] with long-term follow-up found good or excellent outcome after surgery with a mean of 64% (range: 26-100%). A patient satisfaction survey indicated that 37% were much improved and 29% somewhat improved (total: 66%) post-op[339]. A prospective study found a

success rate of 78-88% at 6 wks and 6 months, which dropped to ≈ 70% at 1 year and 5 yrs[340]. Success rates were slightly lower for lateral recess syndrome (*see below*).

LATERAL RECESS SYNDROME

A variant of lumbar stenosis[341]. **Lateral recess**: the “gutter” alongside the pedicle which the nerve root enters just proximal to its exit through the neural foramen (*see Figure 18-4*). It is bordered anteriorly by the vertebral body, laterally by the pedicle, and posteriorly by the superior articular facet of the inferior vertebral body. Hypertrophy of this superior articular facet compresses the nerve root. L4-5 is the most commonly involved facet.

PRESENTATION

Patients develop unilateral or bilateral leg pain predominantly when walking or standing, and usually obtain relief by squatting, sitting with the waist flexed, or lying in the fetal position. Painful burning paresthesias of the lower extremities are also described. Valsalva maneuvers usually do not exacerbate the pain. The time course is usually gradually progressive over many months to years.

In comparison, a HLD usually causes increased pain on sitting, has a more abrupt onset, has pain on straight leg raising, and is worsened by Valsalva maneuvers.

The neurologic exam may be normal (including straight leg raising). Achilles reflexes may be absent.

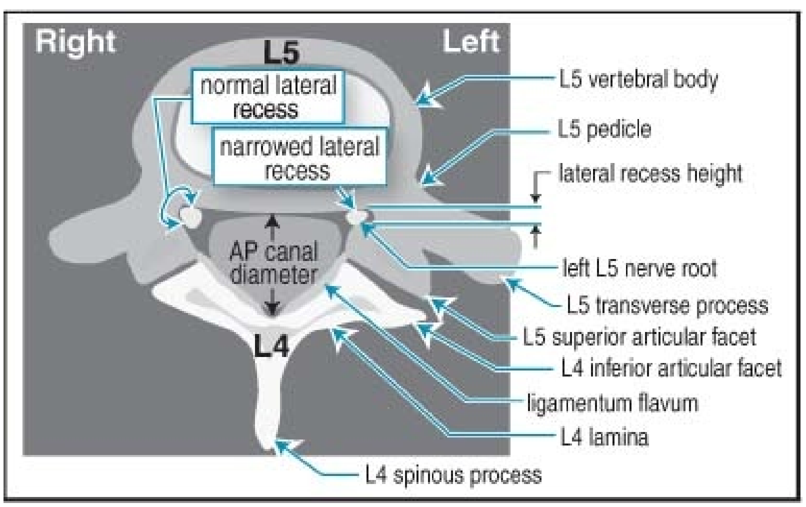

Figure 18-4 Schematic axial CT through the L4-5 facet joint showing the lateral recesses (normal on

patient's right, stenotic on left)

Evaluation

High resolution CT scan best defines the bony anatomy of the lateral recess (*see Figure 18-4* and *Table 18-28*).

MRI or water soluble contrast myelography is recommended when surgery is contemplated. Characteristic finding: flattening of nerve root as it passes beneath the hypertrophied facet joint.

Table 18-28 Dimensions of lateral recess on CT (bone windows)

Lateral recess height	Degree of lateral recess stenosis
3-4 mm	borderline (symptomatic if other lesion co-exists, e.g. disc bulging)
< 3 mm	suggestive of lateral recess syndrome
< 2 mm	diagnostic of lateral recess syndrome

Treatment

Conservative treatment with lumbosacral brace may be attempted.

Surgical therapy

Indicated for unresponsive cases. Consists of laminectomy and partial (typically medial one third) facetectomy. Requires removal of the hypertrophied portion of the facet dorsal to the involved nerve root, either by undercutting, or by reducing overhanging hypertrophied facet elements until they are flush with the pedicle.

18.4.1.2. Cervical spinal stenosis

"**Cervical spondylosis**" is occasionally used synonymously with cervical spinal stenosis. However, spondylosis usually implies a more widespread age-related degenerative condition of the cervical spine including various combinations of the following:

1. congenital spinal stenosis (the "shallow cervical canal"[342])
2. degeneration of the intervertebral disc producing a focal stenosis due to a "**cervical bar**" which is usually a combination of:
   A. osteophytic spurs ("**hard disc**" in neurosurgical jargon)
   B. and/or protrusion of intervertebral disc material ("**soft disc**")
3. hypertrophy of any of the following (which also contributes to canal

stenosis):

  A. lamina
  B. dura
  C. articular facets
  D. ligaments, including
     1. increased stenosis in extension is more common than with flexion (based on MRI studies[343] and cadaver studies), largely due to posterior inbuckling of ligamentum flavum[344]
     2. posterior longitudinal ligament: may include ossification of the posterior longitudinal ligament **(OPLL)**[345] (*see* *page 504*). May be segmental or diffuse. Often adherent to dura
     3. ossification of the ligamentum flavum[316] (yellow ligament)

4. subluxation: due to disc and facet joint degeneration
5. altered mobility: severely spondylotic levels may be fused and are usually stable, however there is often hypermobility at adjacent or other segments
6. telescoping of the spine due to loss of height of VBs → "shingling" of laminae
7. alteration of the normal lordotic curvature[346] (NB: the amount of abnormal curvature did not correlate with the degree of myelopathy)
   A. reduction of lordosis: including
      1. straightening
      2. reversal of the curvature (kyphosis): may cause "bowstringing" of the spinal cord across osteophytes
   B. exaggerated lordosis (hyperlordosis): the least common variant (may also cause bowstringing)

Although the majority of individuals > 50 yrs old have radiologic evidence of significant degenerative disease of the cervical spine, only a small percentage will experience neurologic symptoms[347].

EVALUATION

Cervical spinal stenosis is suggested on plain films when the spinolaminar line is close to the posterior margin of the lateral masses.

CLINICAL

The condition generally tends to produce three types of clinical problems[244]:

1. nerve root compression may cause radicular complaints
2. spinal cord compression may cause myelopathy. Some stereotypical syndromes are presented below (see *Cervical spondylotic myelopathy (CSM)* below)
3. pain and paresthesias in the head, neck and shoulders with little or no suggestion of radiculopathy nor abnormal physical findings. This group is the most difficult to treat, and often requires a good physician-patient relationship to decide if surgical treatment should be undertaken in an attempt to provide relief

CERVICAL SPONDYLOTIC MYELOPATHY (CSM)

Cervical spondylosis is the most common cause of myelopathy in patients > 55 yrs of age[348]. Cervical spondylotic myelopathy (CSM) develops in almost all patients with ≥ 30% narrowing of the cross-sectional area of the cervical spinal canal[349] (although some patients with severe cord compression do not have myelopathy[350, 351]).

PATHOPHYSIOLOGY

Pathogenesis is controversial. Theories include the following alone or in combination:

1. direct cord compression between osteophytic bars and hypertrophy or infolding of the ligamentum flavum, especially if superimposed on congenital narrowing or cervical subluxations
2. ischemia due to compression of vascular structures[352] (arterial deprivation[353] and/or venous stasis[354])
3. repeated local cord trauma by normal movements in the presence of protruded discs and/or osteophytic (spondylotic) bars (cord and root injuries[355])
   A. cephalad/caudad movement with flexion extension[356]
   B. anterior/posterior traction on the cord by dentate ligaments[357] & nerve roots
   C. diameter of spinal canal varies during flexion and extension
      1. increased stenosis is more common in extension (*see above*)
      2. unstable segments may sublux (so-called pincer mechanism)[358]

Histologically[359], there is degeneration of the central grey matter at the level of compression, degeneration of the posterior columns above the lesion

(particularly in the anteromedial portion), and demyelination in the lateral columns (especially the corticospinal tracts) below the lesion. Anterior spinal tracts are relatively spared. There may be atrophic changes in the ventral and dorsal roots and neurophagia of anterior horn cells.

Clinical

Gait disturbance, often with LE weakness or stiffness, is a common early finding in CSM[361]. Cervical pain and mechanical signs are uncommon in cases of pure myelopathy. See *Table 18-29* for the frequency of symptoms in CSM in one series. In most cases the disability is mild, and the prognosis for these is good. CSM is rare in age < 40 years.

Table 18-29 Frequency of symptoms in CSM (37 cases[360])

Finding	%
pure myelopathy	59%
myelopathy + radiculopathy	41%
reflexes	
hyperreflexia	87%
Babinski	54%
Hoffman	13%
sensory deficits	
sensory level	41%
posterior column	39%
dermatomal arm	33%
paresthesias	21%
positive Romberg	15%
motor deficits	
arm weakness	31%
paraparesis	21%
hemiparesis	18%
quadriparesis	10%
Brown-Séquard	10%
muscle atrophy	13%

fasciculations	13%
pain	
radicular arm	41%
radicular leg	13%
cervical	8%
spasticity	54%
sphincter disturbance	49%
cervical mechanical signs	26%

Table 18-30 Modified JOA score for cervical myelopathy[362]*

Score	Description	
Upper extremity (UE) motor dysfunction		
0	unable to feed self	
1	unable to use knife & fork; can eat with spoon	
2	can use knife & fork with much difficulty	
3	can use knife & fork with slight difficulty	
4	none (normal)	
Lower extremity (LE) motor dysfunction		
0	unable to walk	
1	can walk on flat surface with walking aid	
2	can walk up and/or down stairs with handrail	
3	lack of smooth and stable gait	
4	none (normal)	
Sensory deficit		
0	UE	severe sensory loss or pain
1		mild sensory loss
2		none (normal)
0	LE	severe sensory loss or pain
1		mild sensory loss
2		none (normal)
0	trunk	severe sensory loss or pain
1		mild sensory loss
2		none (normal)
Sphincter dysfunction		

0	unable to void
1	marked voiding difficulty (retention)
2	some voiding difficulty (urgency or hesitation)
3	none (normal)

* total score ranges from 0 to 17 (normal)

Grading

1. the modified Japanese Orthopaedic Association scale **(mJOA)** (*Table 18-30*) is a valid and reliable grading system, although it is non-specific
2. **Neck Disability Index** 535: a 10 question survey similar to the Oswestry Disability Index for the lumbar spine (*see page 430*). Mild disability is defined as a score of 10-28%, moderate = 30-48%, severe = 50-68%, complete ≥ 72%
3. other commonly used scales (not tested for validity or reliability):
   A. Nurick[363] (*see page 505*)
   B. Harsh

Natural history

The time course of symptoms is highly variable and unpredictable. In ≈ 75% of cases of CSM, there is progression either in a stepwise fashion (in one third) or gradually progressive (two thirds)[364]. In some series, the most common pattern was that of an initial phase of deterioration followed by a stabilization that typically lasts for years and may not change thereafter[365, 366]. In these cases, the degree of disability may be established early in the course of CSM. Others disagree with such a "benign" outlook and cite that over 50% of cases continue to deteriorate with conservative treatment[347]. Sustained spontaneous improvement is probably rare[348].

In patients < 75 years age and mJOA score > 12 (mild myelopathy), the clinical condition remains stable in 3-years of follow-up (Class I)[367] (however, these patients can still have significant disability that can respond to surgery). Patients with stenosis without myelopathy who have electrodiagnostic abnormalities or clinical radiculopathy are at risk of developing myelopathy (Class I)[367]. Longstanding severe stenosis over many years may cause irreversible deficit due to necrosis in gray and white matter (Class III)[367].

Motor

Findings can be due to cord (UMN) and/or root (LMN) compression. The earliest motor findings are typically weakness in the triceps and hand intrinsics[362]. There may be wasting of the hand muscles[368]. Slow, stiff opening and closing of the fists may occur[369]. Clumsiness with fine motor skills (writing, buttoning buttons…) is common.

There is often proximal weakness of the lower extremities (mild to moderate iliopsoas weakness occurs in 54%) and spasticity of the LEs.

Sensory

Sensory disturbance may be minimal, and when present are often not radicular in distribution. There may be a glove-distribution sensory loss in the hands[370]. A sensory level may occur a number of levels below the area of cord compression.

LEs often exhibit loss of vibratory sense (in as many as 82%), and occasionally have reduced pinprick sensation (9%) (almost always restricted to below the ankle). Compression of the spinocerebellar tract may cause difficulty running. Lhermitte's sign was present in only 2 of 37 cases. Some patients may present with a prominence of posterior column dysfunction (impaired joint position sense and 2 point discrimination)[371].

Reflexes

In 72-87%, reflexes are hyperactive at a varying distance below the level of stenosis. Clonus, Babinski's sign (*see page 116*) or Hoffman's sign (*see page 116*) may also be present. **Dynamic Hoffman's sign**[372] may be more sensitive: test for Hoffman's sign during multiple cervical flexion and extension movements as tolerated by the patient. 94% of asymptomatic individuals with Hoffman's reflex will have significant spinal cord compression on MRI[373]. **Inverted radial reflex**: flexion of the fingers in response to eliciting the brachioradialis reflex, said to be pathognomonic of CSM[374].

A hyperactive **jaw jerk** indicates upper motor neuron lesion above the midpons, and distinguishes long tract findings due to pathology above the foramen magnum from those below (e.g. cervical myelopathy): not helpful if absent (a normal variant). Primitive reflexes (grasp, snout, rooting) are not reliable localizing signs (except perhaps the grasp reflex) of frontal lobe pathology.

Sphincter

Urinary urgency and frequency are common in CSM as well as in the aging population. Urinary incontinence is rare. Anal sphincter disturbances are uncommon.

Syndromes

Clustering of CSM into these 5 clinical syndromes has been described[369]:

1. transverse lesion syndrome: involvement of corticospinal and spinothalamic tracts and posterior columns, with anterior horn cells segmentally involved. Most frequent syndrome, possibly an "end-stage" of the disease process
2. motor system syndrome: primarily corticospinal tract and anterior horn involvement with minimal or no sensory deficit. This creates a mixture of lower motor neuron findings in the upper extremities and upper motor neuron findings (myelopathy) in the lower extremities which can mimic ALS (*see below*). Reflexes may be hyperactive below the area of maximal stenosis (including the upper extremities), occasionally beginning several levels below the stenosis
3. central cord syndrome: motor and sensory deficit affecting the UEs more than the LEs. This syndrome is characterized by dysfunction of the watershed areas located centrally within the cord, which may be responsible for prominence of hand symptoms[375] (results in "**numb-clumsy hands**"[376]). Lhermitte's sign may be more common in this group
4. Brown-Séquard syndrome: often with asymmetric narrowing of the canal with the side of greater narrowing producing ipsilateral corticospinal tract (upper motor neuron weakness) and posterior column dysfunction with contralateral loss of pain and temperature sensation
5. brachialgia and cord syndrome: radicular UE pain with lower motor neuron weakness, and some associated long tract involvement (motor and/or sensory)

Differential diagnosis

See *Myelopathy* on page 1185 for other possible causes. Some of these (e.g. spinal cord tumor, OPLL) may be demonstrated radiographically. Asymptomatic cervical spondylosis is very common, and ≈ 12% of cases of cervical myelopathy attributed to spondylosis are later found to be due to another disease process including:

1. ALS: *see below*
2. multiple sclerosis **(MS)**: spinal cord demyelination may mimic CSM. With MS, remissions and exacerbations are common, and patients tend to be younger
3. herniated cervical disc (soft disc): patients tend to be younger than with CSM. Course is more rapid
4. subacute combined system disease: abnormal vitamin B_{12} level and possibly macrocytic anemia (*see page 1187*)
5. hereditary spastic paraplegia: family history is key. Diagnosis of exclusion[377]
6. (spontaneous) intracranial hypotension (*see page 305*)

Amyotrophic lateral sclerosis (ALS)

AKA (anterior horn) motor neuron disease (also see *Amyotrophic lateral sclerosis*, page 65). Can mimic the motor system syndrome of CSM (*see above*), and spinal cord compression may be seen on MRI in > 60% of patients with ALS[378].

"Triad" of ALS: atrophic weakness of hands and forearms (early), mild LE spasticity, diffuse hyperreflexia. Inevitably, some cases of demyelinating disease will be misdiagnosed initially as CSM until some features suggestive of ALS occur (in one series of 1500 ALS patients, 4% underwent spine surgery (56% cervical, 42% lumbar, 2% thoracic)[378] before ALS was correctly diagnosed).

Features that may help differentiate ALS from CSM:

1. ALS: sensory changes are conspicuously absent
2. ALS: bulbar symptoms (dysarthria, hyperactive jaw-jerk…)[379]
3. ALS: extensive weakness/muscle atrophy of hands, usually with fasciculations[380]
4. ALS: lower-motor neuron **(LMN)** findings in the tongue (visible fasciculations, or positive sharp waves on EMG) or in the LEs (e.g. fasciculations and atrophy) favors the diagnosis of ALS over CSM (however, LMN findings in the LEs may occur in CSM if there is coincidental lumbar radiculopathy)
5. CSM or herniated cervical disc: usually includes neck and shoulder pain, limitation of neck movement, sensory changes, and LMN findings restricted to 1 or 2 spinal cord segments

EVALUATION

Plain x-rays

Plain cervical spine x-rays demonstrates osteophytic spurs, and malalignment if any. See *Canal diameter* on page 136 for normal dimensions and measurement techniques. Patients with CSM have an average minimal AP canal diameter of 11.8 mm[381], and values ≤ 10 mm were likely to be associated with myelopathy[382]. Patients with an AP diameter < 14 mm may be at increased risk[383], and CSM is rare in patients with a diameter > 16 mm, even with significant spurs[348].

Pavlov ratio (AKA Torg ratio[384, 385]): the ratio of the AP diameter of the spinal canal at the mid VB level to the VB at the same location. A ratio < 0.8 is sensitive for transient neuropraxia, but has been shown to have poor positive predictive value for CSM.

MRI

MRI provides information about the spinal canal, and can also show intrinsic cord abnormalities (demyelination, syringomyelia, spinal cord atrophy, edema…). MRI also rules out other diagnostic possibilities (Chiari malformation, spinal cord tumor…). Bony structures and calcified ligaments are poorly imaged. This shortcoming and the difficulties in differentiating osteophytes from herniated discs on MRI are overcome with the addition of plain cervical spine films[386] or thin-section CT bone windows.

Findings that correlate with poor outcome (Class III)[387]:

1. <u>multilevel</u> T2WI hyperintensity within the spinal cord parenchyma
2. <u>single</u> level T2WI hyperintensity with corresponding T1WI hypointensity[A]
3. spinal cord atrophy (transverse area < 45 mm^2)

A. single level T2WI hyperintensity without T1WI changes are of uncertain prognostic significance

Other MRI findings seen with CSM:

1. reduced transverse area of the spinal cord **(TASC)** at the level of maximum compression. A “banana” shaped cord on axial images has a

high correlation with the presence of CSM[383]. There is conflicting evidence whether the *degree* of canal stenosis predicts *outcome*[387]. Sagittal T2WIs tend to exaggerate the magnitude of spinal cord compression by osteophytes and/or discs, and therefore axial images and T1WIs also need to be considered in the evaluation. Narrowing is not specific for CSM: ≈ 26% of asymptomatic individuals > 64 years of age have spinal cord compression on MRI[388]

2. "snake eyes" (AKA "owl's eyes") within the spinal cord on axial T2WI (*see Figure 18-5*) may be related to cystic necrosis of the cord[389] and may correlate with poor outcome (Class III)[387]

CT/myelogram

Plain CT scans may demonstrate a narrow canal, but do not provide adequate information regarding soft tissues (discs, ligaments, spinal cord and nerve roots). Cervical myelography followed by high-resolution CT scanning provides sagittal and axial information (including spinal cord atrophy), and delineates bony detail better than MRI[386]. Unlike MRI, CT/myelogram involves ionizing radiation and does not provide information about changes within the spinal cord parenchyma.

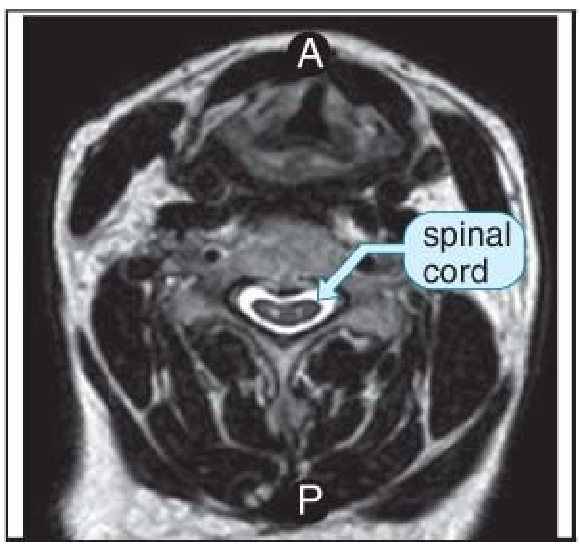

Figure 18-5 Snake eyes (two foci of high signal) within a slightly flattened and mildly atrophic spinal cord on axial T2WI MRI

Sensory evoked potentials (SEPs) - pre-op

Normal pre-op SEPs or normalization of SEPs in the early post-op period are

associated with better outcome[390].

PRACTICE GUIDELINE 18-16 PRE-OP SEPS IN CSM

Pre-op SEPs should be considered if the additional prognostic information would help treatment decisions (**Level B** Class II)[390]

EMG

Not routinely useful in CSM. EMG has poor sensitivity in cervical radiculopathy and is not reliable in predicting outcome from surgery for CSM (Class III)[387]. EMG is most helpful in suspicious cases to eliminate etiologies such as peripheral neuropathy or ALS.

TREATMENT

Indications for surgery

See *PRACTICE GUIDELINE 18-17*.

PRACTICE GUIDELINE 18-17 SURGICAL VS. NONSURGICAL MANAGEMENT

<u>Mild</u> myelopathy (mJOA score > 12)*: in the short-term (3 years) patients may be offered the option of surgical decompression or nonoperative management (prolonged immobilization in a rigid cervical collar, anti-inflammatory medications, and "low-risk" activities or bed rest (**Level C** Class II)[391]

More severe myelopathy: should be treated with surgical decompression with benefits maintained at 5 and 15 years post-op (Level D Class III)[391]

Level B Class I392 Degenerative cervical <u>radiculopathy</u>: patients do better with anterior decompression ± fusion (compared to conservative management) for

- rapid relief (within 3-4 months) of arm & neck pain and sensory loss
- relief of longer term (≥ 12 months) symptoms of weakness of wrist extension, elbow extension, shoulder abduction and internal rotation

* patients with mJOA scores > 12 (see page 487) may not always be mildly impaired, they may derive significant improvement from surgery, and deterioration from this point may be ominous

NONOPERATIVE MANAGEMENT

Measures include: prolonged immobilization with rigid cervical bracing in an attempt to reduce motion and hence the cumulative effects of trauma on the spinal cord, modified activity to eliminate "high-risk" activities or bed rest, and anti-inflammatory medications[393].

SURGICAL TREATMENT

Intraoperative electrophysiologic monitoring

PRACTICE GUIDELINE 18-18 INTRA-OPERATIVE ELECTROPHYSIOLOGIC MONITORING DURING SURGERY FOR CSM OR RADICULOPATHY

Use of intra-op EP monitoring during routine surgery for CSM or cervical radiculopathy is not recommended as an indication to alter the surgical plan or administer steroids since this paradigm has not been observed to reduce the incidence of neurologic injury (**Level D** Class III)[394]

Choice of approach

The debate between anterior approaches (anterior cervical discectomy or corpectomy) and posterior approaches (decompressive cervical laminectomy) dates back to the time that both became widely practiced[244]. General sentiment is to treat anterior disease at the disc level (e.g. osteophytic bar, herniated disc…) usually limited to ≤ 3 levels (or occasionally 4) with an anterior approach, and to use a posterior approach as the initial procedure in the situations outlined below. Considerations of spinal curvature may need to enter into the decision process.

PRACTICE GUIDELINE 18-19 CHOICE OF SURGICAL APPROACH FOR CSM

There was not enough evidence to recommend any of the following techniques over the other (in terms of <u>short-term</u> success in treating CSM): ACDF, anterior corpectomy and fusion, laminectomy (with or without fusion) and laminoplasty ((**Level D** Class III)[395]

Laminectomy without fusion, however, is associated with a higher incidence of late kyphotic deformity* (**Level D** Class III)[395]

* incidence 14-47%, not all cases are symptomatic, not all cases need treatment (see text)

Posterior approach: Options include:

1. laminectomy alone
2. laminectomy/arthrodesis (i.e. laminectomy + lateral mass fusion) (Class III[A 396])
3. laminoplasty (Class III[A 397]): methods include unilateral ("open door") and midline enlargement ("French door")
4. multilevel foraminotomies: usually not adequate for central canal stenosis

A. this procedure was found to be effective, the class shows the strength of the evidence

Situations where a posterior approach would generally be the initial approach:

1. congenital cervical stenosis where removing osteophytes will still not provide at least ≈ 12 mm of AP canal diameter
2. disease over ≥ 3 levels (although up to 4 may occasionally be dealt with anteriorly)
3. primary posterior pathology (e.g. infolding of ligamentum flavum)
4. some cases of OPLL (anterior approach has higher risk of dural tear)

Disadvantages of the posterior approach:

1. laminectomy <u>without</u> fusion
   A. degeneration and osteophytes continue to progress following surgery
   B. risk of subsequent subluxation or progressive kyphotic angulation ("swan neck" deformity)
      1. quoted incidence: 14-47%[398-400] (risk may be minimized by careful preservation of facet joints)
      2. not all cases need to be treated: in one series, 31% (18/58) developed post-op kyphosis, and 16% of these (3/18) required surgical stabilization[401]
      3. the development of kyphotic deformity does not appear to diminish the clinical outcome[400] and does not correlate with neurologic deterioration when deterioration occurs[402].
2. more painful initially post-op and sometimes more prolonged rehabilitation
3. long-term complaints of a heaviness of the head possibly associated with

atrophy of the paraspinal muscles

4. ✖ contraindicated with pre-existing swan neck deformity, and not recommended in the presence of reversal of the normal cervical lordosis (i.e. kyphotic curve)[403] where the spinal cord won't tend to move away from the anterior compression or in the presence of ≥ 3.5 mm subluxation or > 20° rotation in the sagittal plane[383] and caution must be exercised in *hyper* lordosis (*see below*)

Anterior approach: Also shown to be effective (Class III391).

Instrumentation options: in terms of <u>fusion rates</u> for 2-level anterior operations (i.e. 2 disc spaces) (Class III)[395]:

2-level ACDF with anterior plate = 1-level corpectomy with plate > 1-level corpectomy without plate* > 2-level ACDF without plate

* however, the graft extrusion rate is higher for corpectomy than ACDF

Worsening of myelopathy has been reported in 2-5% of patients after anterior decompression[404, 405] (intraoperative SSEP monitoring may reduce this rate[405]) and C5 radiculopathy may occur (*see below*).

Anterior cervical plating:

Many systems are available, with more similarities than differences. All include some method of preventing screw back out. Some general pointers:

1. for single level fusion, typical plate length is 22-24 mm
2. screw length: rule of thumb is 12 mm for females, 14 mm for males
3. do not completely tighten a single screw (to avoid kicking up plate) until the diagonally opposite screws are placed and loosely tightened
4. most systems have fixed and variable angle screws. Variable angle screws allow for load sharing with the graft (here is where a derivative of Wolff's law is often invoked: the weight sharing helps stimulate fusion). Avoid over-angling screws which may prevent the locking mechanism from properly engaging
5. optimal plate placement allows for contact of the plate with the VB at the screw location. This may require
   A. contouring of plate to follow the lordosis of the c-spine
   B. reduction of anterior osteophytes

Posterior approach: For decompression, some recommend cervical laminectomy extending one or <u>two</u> levels beyond the stenosis above and below[406, 407].

Curvature considerations: extending the laminectomy to include C2 and some-times C1 has been recommended for patients with straightening of the cervical curvature[346]. In cases of hyperlordosis, posterior migration of the spinal cord following an extensive laminectomy may put increased tension on the nerve roots and blood vessels (with possible neurologic worsening), and a limited laminectomy just where the cord is compressed is recommended (see *Post-op C5 palsy* below).

"Keyhole foraminotomies" or medial facetectomy with undercutting of the facets may be performed at levels involved with radiculopathy.

Position: choices are primarily: prone, lateral oblique, or sitting. The prone position has a major disadvantage of difficulty elevating the head above the heart, resulting in venous engorgement with significant operative bleeding. The sitting position has a number of inherent risks (see *Sitting position*, page 153) including cord hypoperfusion[405]. The lateral oblique position may introduce some distortion to the anatomy due to asym-metrical positioning.

The rate of post-op spinal deformity is 25-42%. Neurologic worsening has been reported in 2% in some series, higher in others. C5 radiculopathy may occur (*see below*).

To avoid significant destabilization of the cervical spine:

1. during the dissection, do not remove soft tissue overlying the facet joints (to preserve their blood supply)
2. take the laminectomy only as far lateral as the extent of the spinal canal, carefully preserving the facet joints[347] (use keyhole laminotomies where necessary)
3. avoid removing a total of one facet at any given level

OUTCOME

Even excluding cases that are later proven to have demyelinating disease, the outcome from surgery for CSM is often disappointing. Once CSM is clinically apparent, complete remission almost never occurs. The prognosis with surgery is worse with increasing severity of involvement at the time of presentation[406] and with longer duration of symptoms (48% showed clinical improvement or cure if operated within 1 yr of onset, whereas only 16% responded after 1 yr[347]). The success of surgery is also lower in patients with other degenerative diseases of the CNS (ALS, MS…).

Progression of myelopathy may be arrested by surgical decompression. This is not always borne out, and some early series[363, 366] showed similar results with

conservative treatment as with laminectomy which yielded improvement in 56%, no change in 25%, and worsening in 19%. Also as discussed earlier (see *Natural history*, page 487) some cases of CSM develop most of the deficit early and then stabilize.

Some series show good results, with ≈ 64-75% patients having improvement in CSM post-op[360]. However, other authors remain less enthusiastic. Utilizing a questionnaire in 32 post-op patients operated anteriorly, 66% had relief from radicular pain, while only 33% had improvement in sensory or motor complaints[360]. In one series, half the patients had improvement in fine motor function of the hands, but the other half worsened postoperatively[408]. Spinal cord atrophy as a result of continued pressure or ischemia may be partly responsible for poor recovery. Bedridden patients with severe myelopathy rarely recover useful function.

Post-op C5 palsy: Criteria: weakness of deltoid and/or biceps with no worsening of myelopathy. Follows ≈ 3-5% of extensive anterior or posterior decompression (including laminoplasty)[404, 409]. 50% have motor involvement only (deltoid > biceps), 50% also have C5 dermatomal sensory loss and/or C5 dermatomal pain (shoulder). Most occur < 1 week post-op[409]. 92% are unilateral[409]. No pre-op risk factors have been identified[410]. Etiology: unproven, may be related to traction on the nerve root from posterior migration of the cord after decompression or to bone graft displacement. Prognosis for spontaneous recovery is generally good; more severe deficits take longer to recover[409].

Late developments:

Some patients who show early improvement will develop late deterioration (7-12 yrs after reaching a plateau)[383], with no radiographically apparent explanation in up to 20% of these cases[411]. In others, degeneration at levels adjacent to the operated segments may be demonstrated.

Adjacent segment disease (ASD): degeneration that develops at a motion segment adjacent to a previous fusion. Findings include: disc degeneration, stenosis, facet hypertrophy, scoliosis, listhesis and instability. After ACDF, ASD occurred at a rate of 2.9% per year over 10 years observation[412]. Estimate: 25% of patients will develop symptomatic adjacent level changes within 10 years of surgery[412]. This rate was higher with single level fusion at C5-6 or C6-7 than it was with multilevel fusion, and natural progression of the disease was felt to be a significant contributor[412] (i.e. it was not all attributable to the fusion). Most cases of ASD observed radiographically are asymptomatic

18.4.1.3. Coincident cervical and lumbar spinal stenosis

Coincident symptomatic lumbar and cervical spinal stenosis is usually managed by first decompressing the cervical region, and later operating on the lumbar region (unless severe neurogenic claudication dominates the picture). It is also possible, in selected cases, to operate on both in a single sitting[304, 413].

18.5. Craniocervical junction and upper cervical spine abnormalities

Also see *Axis (C2) vertebra lesions*, page 1231.

ASSOCIATED CONDITIONS

Abnormalities in this region are seen in a number of conditions including:

1. rheumatoid arthritis: *see page 494*
2. traumatic & post-traumatic: including fractures of odontoid, occipital condyles…
3. **ankylosing spondylitis**: (*see page 502*) may result in fusion of the entire spine which spares the occipitoatlantal and/or atlantoaxial joints which can lead to instability there
4. congenital conditions:
   A. Chiari malformations: *see page 233*
   B. Klippel-Feil syndrome: *see page 253*
   C. Down syndrome
   D. atlantoaxial dislocation **(AAD)**
   E. occipitalization of the atlas: seen in 40% of congenital AAD[414]
   F. Morquio syndrome (a mucopolysaccharidosis): atlantoaxial subluxation occurs due to hypoplasia of the odontoid process and joint laxity
5. neoplasms: metastatic (*see page 743*) or primary
6. infection
7. following surgical procedures of the skull base or cervical spine: e.g. transoral resection of the odontoid

TYPES OF ABNORMALITIES

Abnormalities include:

1. basilar impression/invagination: as with Paget's disease
2. atlanto-occipital dislocation
3. atlantoaxial dislocation
4. occipitalization of the atlas, or thin or deficient posterior arch of atlas[415]

Treatment

Fractures of the occipital condyles, atlas or axis are usually adequately treated with external immobilization (also see *Occipital condyle fractures*, page 954). Because traumatic occipitocervical dislocations are usually fatal, optimal treatment is not well defined. Occipitalization of the atlas may be treated by creating an "artificial atlas" from the base of the occiput and wiring to that[415].

Indications and techniques are outlined in *Atlantoaxial fusion (C1-2 arthrodesis)* on page 183.

18.6. Rheumatoid arthritis

More than 85% of patients with moderate or severe rheumatoid arthritis **(RA)** have radiographic evidence of C-spine involvement[416].

The grading system of Ranawat et al.[416] for myelopathy is shown in *Table 18-31* is used in RA as well as other etiologies of myelopathy.

Table 18-31 Ranawat classification of myelopathy

Class	Description
I	no neural deficit
II	subjective weakness + hyperreflexia + dysesthesia
III	objective weakness + long tract signs III A = ambulatory III B = quadriparetic & non ambulatory

Common cervical spine involvement in RA:

1. upper cervical spine: involved in 44-88% of RA cases[417] (often found together):
   A. anterior **atlantoaxial subluxation**: the most common manifestation of RA in the cervical spine, found in up to 25% of patients with RA (*see below*)

B. **basilar impression (BI)**: upward translocation of the odontoid process, found in ≈ 8% of patients with RA (*see page 497*)
C. pannus of granulation tissue: forms around the odontoid
2. subaxial C-spine (i.e. below C2): subluxation (*see page 498*)

Less common involvement of the cervical spine in RA:

1. posterior subluxation of the atlantoaxial joint: must have either associated fracture of or near total arthritic erosion of odontoid
2. vertebral artery insufficiency secondary to changes at cranio-cervical junction[418]

18.6.1. Atlantoaxial subluxation (AAS) in RA

Inflammatory involvement of the atlantoaxial synovial joints causes erosive changes in the odontoid process (anteriorly at the synovial joint with the C1 arch, and posteriorly at the synovial joint with the transverse ligament) and decalcification and loosening of the insertion of the transverse ligament on the atlas. These changes lead to instability allowing a scissoring effect with anterior subluxation of C1 on C2. AAS occurs in ≈ 25% of patients with RA[418]. Mean time between onset of RA symptoms to the diagnosis of AAS in 15 patients: 14 years[419].

CLINICAL

Signs and symptoms of AAS are shown in *Table 18-32*.

AAS is usually slowly progressive. Mean age at onset of AAS symptoms: 57 years.

Pain is experienced locally (upper cervical and suboccipital regions, often from compression of C2 nerve root) or is referred (to mastoid, occipital, temporal, or frontal regions).

VBI may occur from VA involvement (*see page 1158*).

Table 18-32 Signs and symptoms of AAS* (15 patients with AAS[419])

Finding	%
pain	
local	67%
referred	27%

hyperreflexia	67%
spasticity	27%
paresis	27%
sensory disturbance	20%

* other possible findings not reported in this series: clumsiness, neurogenic bladder, Babinski sign

Radiographic evaluation

The magnitude of AAS is usually increased with neck flexion.

Lateral C-spine x-ray

Anterior atlantodental interval (ADI)

The ADI (*see page 957* for details) only gives information about the *stability* of the C1-2 joint. The normal ADI in adults is < 3-4 mm[420, 421]. Widening of the ADI suggests possible incompetence of the transverse ligament. However, the ADI does not correlate with the risk of neurologic injury[422, 423] and is not predictive of progression from asymptomatic AAS to symptomatic AAS.

Posterior atlantodental interval (PADI)

The amount of room available for the spinal cord can vary for any given ADI depending on the AP diameter of the spinal canal and the thickness of any pannus. The PADI (*see page 136*) and the AP diameter of the *subaxial* canal measured on a lateral C-spine x-ray correlates with the presence and severity of paralysis[422].

The PADI also predicts neurologic recovery following surgery. Patients with paralysis from AAS showed no recovery if the pre-op PADI was < 10 mm[422].

PADI ≤ 14 mm has been proposed as an indication for surgical stabilization.

MRI

The optimal test to evaluate the source and magnitude of upper cord or medulla compression. Demonstrates location of odontoid process, extent of pannus, and effects of subluxation (may need to be performed with head flexed to evaluate this).

Treatment

Requires knowledge of the following information:

- natural history: AAS in most patients progresses, with a small percentage either stabilizing or fusing spontaneously. In one series[424] with 4.5 years mean followup, 45% of patients with 3.5-5 mm subluxation progressed to 5-8 mm, and 10% of these progressed to > 8 mm
- once myelopathy occurs, it may be irreversible
- the worse the myelopathy, the higher the risk for sudden death
- the chances of finding myelopathy are significantly increased once the subluxation reaches ≥ 9 mm[425]
- associated cranial settling further decreases the tolerance for AAS
- life expectancy of patients with RA is 10 years less than the general population[424]
- the morbidity and mortality of surgical treatment (*see below*)
- pannus may regress some after medical treatment

When to treat?

- symptomatic patients with AAS: almost all require surgical treatment (C1-2 fusion in most cases). For management, *see below*
  A. some surgeons do not operate if the maximal dens-C1 distance is < 6 mm
- asymptomatic patients: controversial
  A. some authors feel surgical fusion is not necessary in asymptomatic patient if the dens-C1 distance is below a certain cutoff. Recommendations for this cutoff have ranged from 6 to 10 mm[426], with **8 mm** commonly cited (an un-validated delineation)
  B. these patients are often placed in a rigid cervical collar, e.g. while outside the home, even though it is generally acknowledged that a collar probably does not provide significant support or protection
  C. NB: some cases of sudden death in previously asymptomatic RA patients may be due to AAS and may then be erroneously attributed to cardiac arrhythmias, etc.[427]

Surgical management

It is necessary to either reduce the subluxation or to decompress the upper cord before doing a C1-C2 or occipital-C1-C2 fusion.

Menezes assesses all subluxed patients for reducibility using MRI

compatible Halo cervical traction as follows: start with 5 lbs, and gradually increase over a period of a week. Most cases reduce within 2-3 days. If not reduced after 7 days then it is probably not reducible. Only ≈ 20% of cases are not reducible (most of these have odontoid > 15 mm above foramen magnum).

Most require stabilization via posterior wiring and fusion, either of C1 to C2, or of occiput to C2. The latter is used when fusion is combined with decompression (posterior laminectomy of C1 with posterior enlargement of the foramen magnum). See *Atlantoaxial fusion (C1-2 arthrodesis)* on page 183.

Posterior fusion alone does not provide adequate relief if the subluxation is irreducible, or if pannus causes significant compression (however, there may be some reduction of pannus after fusion). In these cases, transoral odontoidectomy may be indicated. Performing the posterior stabilization and decompression first allows some patients to avoid a second operation, and permits the remainder to undergo the anterior approach without becoming destabilized. Still, some surgeons do the odontoidectomy first[426] (requires the patient to remain in traction until the fusion).

Reminder: the patient must be able to open the mouth greater than ≈ 25 mm in order to perform transoral odontoidectomy without splitting the mandible.

Posterior fusion

See *Atlantoaxial fusion (C1-2 arthrodesis)* on page 183 for technique. In RA, erosion and osteoporosis weakens the C1 arch, and extra care is needed to avoid fracturing it.

Morbidity and mortality

Because of the frequency of simultaneous involvement of other systems in RA including pulmonary, cardiac, and endocrine, operative mortality ranges from 5-15%[426].

The non-fusion rate for C1-2 wiring and fusion has been reported as high as 50%[428], typical rates are lower (with 18% of patients in one series developing a fibrous union[426]). The most common site of failure of osseous fusion is the interface between the bone graft and the posterior arch of C1429.

Post-operative care

The patient is usually mobilized almost immediately post-op in halo vest traction (some use an optional period of maintained traction before mobilization). Impaired healing in RA dictates that the Halo be worn until fusion

is well established, as seen on x-ray (usually 8-12 weeks). Sonntag evaluates the patient with flexion-extension lateral C-spine x-rays by disconnecting the halo ring from the vest.

18.6.2. Basilar impression in rheumatoid arthritis

AKA atlantoaxial impaction. Erosive changes in the lateral masses of C1 → telescoping of the atlas onto the body of C2 causing ventral migration of C1 with resultant ↓ in AP diameter of the spinal canal. There is concomitant upward displacement of the dens. The posterior arch of C1 often protrudes superiorly through the foramen magnum. All of these factors lead to compression of the pons and medulla. Rheumatoid granulation tissue behind the odontoid also contributes. Vertebral artery and/or anterior spinal artery compression may also cause neurologic dysfunction.

The degree of erosion of C1 correlates with the extent of odontoid invagination.

CLINICAL

See Table 18-33 for signs & symptoms.

Pain may occur as a result of compression of the C1 and/or C2 nerve roots. Compression of the medulla can cause cranial nerve dysfunction.

Motor exam usually difficult because of severe polyarticular degeneration and associated pain. Sensory findings (all non-localizing): diminished vibratory, position, and light touch.

Table 18-33 Symptoms and signs of BI (45 patients with RA[417])

Finding	%
headache	100%
progressive difficulty ambulating	80%
hyperreflexia + Babinski	80%
limb paresthesias	71%
neurogenic bladder	31%
cranial nerve dysfunction	22%
trigeminal nerve anesthesia	20%
glossopharyngeal	
vagus	

hypoglossal	
miscellaneous findings	
internuclear ophthalmoplegia	
vertigo	
diplopia	
downbeat nystagmus	
sleep apnea	
spastic quadriparesis	

RADIOGRAPHIC EVALUATION

See *Basilar invagination & basilar impression (BI)* on page 138 for radiographic criteria of BI. Erosion of the tip of the odontoid, commonly seen in RA, obviates use of any measurement that is based on the location of the tip of the odontoid[430]. For this reason, other measures have been developed, including the Clark station[429], Redlund-Johnell criteria[431], and Ranawat criteria[416]. Since even these methods will miss up to 6% of cases of BI in RA[430], it is recommended that suspicious cases be investigated further (e.g. with CT and/or MRI).

MRI: optimal for demonstrating brain stem impingement, poor for showing bone. **Cervicomedullary angle**: the angle between a line drawn through the long axis of the medulla on a sagittal MRI and a line drawn through the cervical spinal cord. The normal CMA is 135-170°. A CMA < 135° correlates with signs of cervicomedullary compression, myelopathy or C2 radiculopathy[432].

CT: primarily done to assess bony anatomy (erosion, fractures…).

CTA should be performed when surgery is contemplated, to show VA anatomy.

Myelography (water soluble) with CT: also good for delineating bony pathology.

TREATMENT

See also *Craniocervical junction and upper cervical spine abnormalities* on page 494.

CERVICAL TRACTION

May attempt with Gardner-Wells tongs. Begin with ≈ 7 lbs, and slowly increase up to 15 lbs. Some may require several weeks of traction to reduce.

SURGERY

Reducible cases: posterior occipitocervical fusion ± C1 decompressive laminectomy. Irreducible cases: requires transoral resection of odontoid. May perform before posterior fusion (but then must be kept in traction while waiting for posterior fusion).

18.6.3. Subaxial subluxation in rheumatoid arthritis

The direct effects of RA on the subaxial spine involves the facet joints posteriorly. Degenerative disc disease, which is generally a late manifestation in RA, is not the result of synovitis[433]. Involvement is most common at C2-3 and C3-4.

18.7. Atlantoaxial subluxation (AAS) in Down syndrome

No all cases of AAS are *unstable* (which, by definition, needs treatment).

Incidence of AAS in Down syndrome **(DS)** is 20% 434, but only 1-2% of DS patients have symptomatic AAS[435]. AAS in DS appears to be due to laxity of the transverse atlantal ligament **(TAL)**. This laxity may decrease with age as the TAL stiffens.

Management

Controversial. There have been position statements[436] and rebuttals[435, 437].

Recommendations (modified[438]):

1. children who have been screened and do not have AAS: no further screening after age 10 years (since AAS does not develop later; the cutoff age is controversial)
2. **os odontoideum**: surgical fusion
3. **symptomatic AAS**
   A. symptoms may include: gait difficulties, neck pain, limited neck motion, torticollis, clumsiness, sensory deficits, and other symptoms of myelopathy
   B. for ADI[A] > 4.5 mm or PADIA < 14 mm or spinal cord damage on cervical MRI: surgical fusion

4. **asymptomatic AAS** seen on lateral C-spine x-ray:
   A. for ADI ≤ 4.5 mm <u>and</u> PADI ≥ 14 mm: no need for further testing
   B. for ADI > 4.5 mm or PADI < 14 mm: cervical MRI
      1. if the MRI shows spinal cord damage: surgical fusion
      2. if MRI shows no spinal cord damage: surgical fusion is optional. If fusion is not done, prohibit high-risk activities and restudy in 1 year

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A. **ADI** = atlantodental interval (*see page 136*), **PADI** = posterior atlantodental interval (*see page 136*)

18.8. Paget's disease

PATHOPHYSIOLOGY

Paget's disease **(PD)** (AKA osteitis deformans) is a disorder of osteoclasts (possibly virally induced) causing increased rate of bone resorption with reactive osteoblastic overproduction of new, weaker, woven bone, producing characteristic "**mosaic pattern**".

Initially there is a "hot" phase with elevated osteoclastic activity and increased intraosseous vascularity. Osteoblasts lay down a soft, nonlamellar bone. Later a "cool" phase occurs with disappearance of the vascular stroma and osteoblastic activity leaving sclerotic, radiodense, brittle bone[439] ("**ivory bone**").

Malignant degeneration

A misnomer, since the malignant changes actually occur in the reactive osteoblastic cells. About 1% (reported range: 1-14%) degenerate into sarcoma (osteogenic sarcoma, fibrous sarcoma, or chondrosarcoma)[440 (p 2642)], with the possibility of systemic (e.g. pulmonary) metastases. Malignant degeneration is much less common in the spine than in the skull or femur.

EPIDEMIOLOGY

Prevalence: ≈ 3% of population > 55 years old in the U.S. and Europe[441]. Slight male predominance. Family history of Paget's disease is found in 15-30% of cases (accuracy is poor since most are asymptomatic).

Common sites of involvement

Affinity for axial skeleton, long bones and skull. In approximate descending order of frequency: pelvis, thoracic and lumbar spine, skull, femur, tibia, fibula, and clavicles.

PRESENTATION

Only ≈ 30% of pagetic sites are symptomatic[442], the rest are discovered incidentally. The overproduction of weak bone may produce bone pain (the most common symptom), predilection for fractures and compressive syndromes (cranial nerve (*see page 1204*), spinal nerve root…). Painless bowing of a long bone may be the first manifestation. A number of patients present due to pain from joint dysfunction related to PD.

NEUROSURGICAL INVOLVEMENT

PD may present to the neurosurgeon as a result of:

- back pain: usually not as a direct result of vertebral bone involvement (*see below*)
- spinal cord and/or nerve root symptoms
  - compression of the spinal cord or cauda equina (relatively rare)
  - spinal nerve-root compression
  - vascular steal due to reactive vasodilatation adjacent to involved areas
- with skull involvement:
  - compression of cranial nerves as they exit through bony foramina (8th nerve is most common, producing deafness or ataxia): *see page 1204*
  - skull base involvement → basilar invagination
- to ascertain diagnosis in unclear bone lesions of the spine or skull

EVALUATION

1. lab work (markers may be normal in monostotic involvement):
   A. serum alkaline phosphatase: usually elevated (this enzyme is involved in bone synthesis and so may not be elevated in purely lytic Paget's disease[100 (p 1416)]); mean 380 ± 318 IU/L (normal range: 9-44)[443]. Bone-specific alkaline phosphatase may be more sensitive and may be useful in monostotic involvement[441]
   B. calcium: usually normal (if elevated, one should R/O hyperparathyroidism)

   C. urinary hydroxyproline: found almost exclusively in cartilage. Due to the high turnover of bone, urinary hydroxyproline is often increased in PD with a mean of 280 ± 262 mg/24 hrs (normal range 18-38)[443]
2. bone scan: lights up in areas of involvement in most, but not all[443] cases
3. plain x-rays:
   A. localized enlargement of bone: a finding unique to PD (not seen in other osteoclastic diseases, such as prostatic bone mets)
   B. cortical thickening
   C. sclerotic changes
   D. osteolytic areas (in skull → osteoporosis circumscripta; in long bones → “V” shaped lesions)
   E. spinal Paget’s disease often involves <u>several contiguous levels</u>. Pedicles and lamina are thickened, vertebral bodies are usually dense and compressed with increased width. Intervening discs are replaced by bone
4. CT: hypertrophic changes at the facet joints with coarse trabeculations

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18.8.1. Paget’s disease of the spine

PRESENTATION

The overwhelming majority of pagetic lesions are asymptomatic[100] (p 1413) with lesions detected on radiographs or bone scan obtained for other reasons or as part of a work-up for an elevated alkaline phosphatase. Although the most common complaint in patients with Paget’s disease is of back pain, this is attributable to pagetic involvement alone in only ≈ 12%[443], in the remainder it is secondary to other factors, some of which are described below.

Symptoms that may be related to the Paget’s disease itself:

1. symptoms from the following are slowly progressive (usually present for > 12 months; rarely < 6 mos)
   A. neural compression
      1. causes of compression
         a. due to expansion of woven bone
         b. due to osteoid tissue
         c. pagetic extension into ligamentum flavum and epidural fat[444]
      2. sites of compression
         a. spinal cord (*see below*)

b. nerve root in neural foramen

B. osteoarthritis of facet joints (Paget's disease may precipitate osteoarthritis[443])

2. symptoms from the following tend to progress more rapidly

A. malignant (sarcomatous) change of involved bone (rare, *see above*)

B. pathologic fracture (pain usually sudden in onset)

C. neurovascular (compromise of vascular supply to nerves or spinal cord) by

1. compression of blood vessels (arterial or venous)

2. pagetic vascular steal (*see below*)

Spinal cord symptoms

Myelopathy or cauda equina syndrome may be due to spinal cord compression or from vascular effects (occlusion, or "steal" due to reactive vasodilatation of nearby blood vessels[100 (p 1415)]). Only ≈ 100 cases had been described as of 1981445. Characteristically, 3-5 adjacent vertebrae are involved[446 (p 2307)], whereas monostotic involvement is usually asymptomatic[447]. In case reports in the literature, progressive quadri- or paraparesis was the most common presentation[448]. Sensory changes are usually the first manifestation, progressing to weakness and sphincter disturbance. Pain was the only symptom in a neurologically intact patient in only 5.5%.

A rapid course (averaging 6 wks) with a sudden increase in pain is more suggestive of malignant degeneration.

TREATMENT

MEDICAL TREATMENT FOR PAGET'S DISEASE

There is no cure for Paget's disease. Medical treatment is indicated for cases that are not rapidly progressive where the diagnosis is certain, for patients who are poor surgical candidates, and pre-op if excessive bleeding cannot be tolerated. Medical therapy reverses some neurologic deficit in 50% of cases[449], but generally requires prolonged treatment (≈ 6-8 months) before improvement occurs, and may need to be continued indefinitely due to propensity for relapses. Medications used include the following.

Calcitonin derivatives

Parenteral salmon **calcitonin** (Calcimar®)[449]: reduces osteoclastic activity directly, osteoblastic hyperactivity subsides secondarily. Relapse may occur even while on calcitonin. Side effects include nausea, facial flushing, and the development of antibodies to salmon calcitonin (these patients may benefit from a more expensive synthetic human preparation (Cibacalcin®) starting at 0.5 mg SQ q d[450]).

Rx 50-100 IU (medical research council units) SQ q d **x** 1 month, then 3 injections per week for several months[441]. If used pre-op to help decrease bony vascularity, ≈ 6 months of treatment is ideal. Doses as low as ≈ 50 IU units 3 **x** per week may be used indefinitely post-op or as a sole treatment (alkaline phosphatase and urinary hydroxyproline decline by 30-50% in > half of patients in 3-6 months, but they rarely normalize).

Bisphosphonates

These drugs are pyrophosphate analogues that bind to hydroxyapatite crystals and inhibit reabsorption. They also alter osteoclastic metabolism, inhibit their activity, and reduce their numbers. They are retained in bone until it is resorbed. Oral absorption of all is poor (especially in the presence of food). Bone formed during treatment is lamellar rather than woven.

Etidronate (Didronel®) (AKA EHDP): reduces normal bone mineralization (especially at doses ≥ 20 mg/kg/d) producing mineralization defects (osteomalacia) which may increase the risk of fracture but which tend to heal between courses[451]. Contraindicated in patients with renal failure, osteomalacia, or severe lytic lesions of a LE. ***Rx*** 5-10 mg/kg PO daily (average dose: 400 mg/d, or 200-300 mg/d in frail elderly patients) for 6 months, may be repeated after a 3-6 month hiatus if biochemical markers indicate relapse.

Tiludronate (Skelid®): unlike etidronate, does not appear to interfere with bone mineralization at recommended doses. Side effects: abdominal pain, diarrhea, N/V. ***Rx*** 400 mg PO qd with 6-8 ounces of plain water > 2 hrs before or after eating **x** 3 months. Available: 200 mg tablets.

Pamidronate (Aredia®): much more potent than etidronate. May cause a transient acute flu-like syndrome. Oral dosing is hindered by GI intolerance, and IV forms may be required. Mineralization defects do not occur in doses < 180 mg/course. ***Rx*** 90 mg/d IV **x** 3 days, or as weekly or monthly infusions.

Alendronate (Fosamax®): does not produce mineralization defects (*see page 994*).

Clodronate (Ostac®, Bonefos®): ***Rx*** 400-1600 mg/d PO **x** 3-6 months. 300 mg/d IV **x** 5 days.

Risedronate (Actonel®): does not interfere with bone mineralization in recommended doses[452]. ***Rx***: 30 mg PO q d with 6–8 oz. of water at least 30 minutes before the first meal of the day.

Under development: ibandronate, neridronate, and others.

Plicamycin

Formerly mithramicin. A cytotoxic antibiotic that inhibits RNA synthesis with preferential toxicity for osteoclasts. Reserved for severe and extensive involvement due to dose dependent renal and hepatic impairment and possible thrombocytopenia. Not approved for treating Paget's disease in any country.

Rx 15-25 µg/kg given IV over 8-10 hours qod **x** 10 infusions.

SURGICAL TREATMENT

In general, conservative treatment of fractures in PD have a high rate of delayed union.

Surgical indications for spinal Paget's disease

1. rapid progression: indicating possible malignant change or spinal instability
2. spinal instability: severe kyphosis or compromise of canal by bone fragments from pathologic fracture. Although the collapse is usually gradual, sudden compression may occur
3. uncertain diagnosis: especially to R/O metastatic disease (osteoblastic lesions)
4. failure to improve with medications

Surgical considerations:

1. profuse bleeding is common: if significant bleeding would present an unusual problem, treat for as long as feasible pre-op with a bisphosphonate or calcitonin (*see above*)
   A. use bone wax to help control bleeding
   B. hemostasis may be difficult
2. to treat resultant spinal stenosis: decompressive laminectomy is the standard procedure in the thoracic region[448]. However, if most of the pathology is anterior, consideration should be given to anterior approach
3. bone is often thickened, and may be fused with obliteration of interspace landmarks. A high-speed drill is usually helpful

4. post-op medical treatment may be necessary to prevent recurrences[449]
5. osteogenic sarcoma
   A. surgery and chemotherapy are used, cure is less likely than in primary osteosarcoma of non-pagetic origin
   B. biopsy proven of the scalp requires en-bloc excision of scalp and tumor

Surgical outcome[448]:

In 65 patients treated with decompressive laminectomy, 55 (85%) had definite but variable degrees of improvement. Patients who had only minimal improvement were often ones with malignant changes. One patient was worse after surgery, and the operative mortality was 7 patients (10%). Survival with malignant degeneration is < 5.5 mos after admission.

18.9. Ankylosing spondylitis

Key concepts:

> • a seronegative spondylarthropathy (enthesopathy)
> • starts in the SI joints and progresses rostrally
> • clinical: morning back stiffness, kyphoscoliosis limits chest expansion
> • x-ray findings: "bamboo spine", Andersson lesions, progressive thoracic kyphosis
> • risk of SCI due to fracture is increased, and may follow minimal trauma

AKA Marie-Strümpell disease. Ankylosing spondylitis **(AS)**: one of the so-called seronegative arthropathies (ANA and serum rheumatoid factor are negative[453], unlike rheumatoid arthritis). The spine is the primary skeletal site involved, usually starting in the sacroiliac joints and lumbar spine and progressing rostrally. **Enthesopathy**: nongranulomatous inflammatory changes at the entheses (attachment points of ligaments, tendons or capsules on bones; the locus of involvement in AS) stimulates replacement of ligaments by bone ultimately resulting in osteoporotic VBs, calcified intervertebral discs (sparing the nucleus pulposus), and ossified ligaments, producing square appearing VBs with bridging syndesmophytes, the so-called "**bamboo spine**" or "poker spine".

Differential diagnosis:

1. early on, AS may resemble rheumatoid arthritis. However, in AS nodules do not form in joints, and rheumatoid factor is absent in the serum
2. metastatic prostate Ca in elderly male patients with sacroiliac pain and blastic changes compatible with sacroiliitis
3. Forestier's disease (*see page 506*) and DISH (*see page 506*): these overlapping conditions produce exuberant bony overgrowth anterior and lateral to the disc without degeneration and ossification of the disc as in AS. Both spare the facets and SI joints, do not produce flexion deformity, and tend to occur in men > 50 yrs old (older than typical AS)[453]
4. psoriasis and Reiter's syndrome: spondylitis tends to be milder and less uniform and SI joint involvement is asymmetrical

EPIDEMIOLOGY

Incidence is ≈ 1-3 cases per 100,000. Symptoms tend to be more pronounced in males, which has resulted in an underreporting of the condition in females and an exaggeration of the estimation of the male predominance (incidence is probably ≈ equal)[454]. Peak incidence: 17-35 yrs age. Although AS is not hereditary, first degree relatives are at increased risk.

DIAGNOSTIC CRITERIA

Modified New York criteria (*see Table 18-34*) may not be helpful for diagnosis early on. SI joint involvement is the sine qua non for definite diagnosis.

CLINICAL

Typical initial presentation is with nonradiating low back pain, morning back stiffness, hip pain and swelling (due to large joint arthritis), exacerbated by inactivity and improved with exercise[455]. **Patrick's test** (*see page 444*) usually positive. Compressing the pelvis with the patient in the lateral decubitus position produces pain. **Schober test** (measure distraction between skin marks on the back with forward flexion to detect reduced mobility of the spine due to fusion[46]) is not specific for inflammatory spondylopathies[456] but may be helpful for monitoring ongoing physical therapy.

Table 18-34 Modified New York Criteria for AS

Diagnosis (see criteria below)
Definite AS: radiologic criterion + ≥ 1 clinical criteria

Probable AS: radiological criterion without clinical criteria, or 3 clinical criteria without radiological criterion
Clinical criteria
low back pain > 3 months, improved by exercise, not relieved by rest
limitation of lumbar spine motion in both sagittal and frontal planes
limitation of chest expansion relative to normal values for age and sex
Radiological criterion
sacroiliitis

Neurosurgical involvement usually results from the following:

1. cauda equina syndrome **(CES)**: etiology is frequently unclear, but is usually not due to stenosis or compressive lesion. In the absence of compression, surgical intervention is not indicated
2. rotatory subluxation: at occipito-atlantal and atlanto-axial joints. May occur as these are typically the last mobile segments of the spine. Incidence is much less than with rheumatoid arthritis. Lesions that might be stable in otherwise normal spines are often not stable in AS
3. myelopathy secondary to bow-stringing of the cord: laminectomy may aggravate
4. acute spinal cord injury **(SCI)**: risk of SCI or CES due to fracture is increased in AS, and may occur following minimal trauma. Injuries are more common in the lower cervical spine. The rigid spine of AS when fractured acts as a long lever and is extremely unstable[457]. Delayed deterioration may be due to spinal epidural hematoma[458]
5. vertebral stress fractures: most common in the lower thoracic and upper lumbar spines, usually through the ossified intervertebral disc ("**chalk-stick**" fracture)
6. painful pseudarthroses
7. spinal deformity
8. spinal stenosis: rare
9. basilar impression

Radiographic evaluation

Plain x-rays: vital for diagnosis and follow-up. Sacroiliac **(SI)** joint involvement (on AP pelvic x-rays or on oblique views through the plane of the SI joints) is one of the earliest findings, and the often symmetric osteoporosis followed by sclerosis is characteristic. "Bamboo spine" (*see above*) is also

classic. X-ray of the entire spine is recommended since multiple, non-contiguous (and often unsuspected) fractures are not unusual.

MRI: can rule out spinal epidural hematoma and the occasional herniated disc. **Andersson lesions**: pathologic changes at ligament insertion sites (MRI signal abnormalities at front and back of the endplates) are characteristic. Erosive changes due to pseudarthrosis at the disc space can mimic discitis (hi signal on T1WI & T2WI with enhancement).

Bone scan: ratio of uptake of SI joint to sacrum > 1.3:1 is suggestive of AS.

Natural history

Progression is slow, and patients usually remain functionally active. Thoracic kyphosis with compensatory increase in cervical and lumbar lordosis is common. The shift in center of gravity together with spine stiffness and fragility predisposes to frequent falls and further spine injuries.

Treatment

Management of the disease itself may involve use of immune modulators.

Surgical considerations

Aspects of AS than may increase anesthetic risk:

1. difficulty intubating due to fragile, angulated & immobile spine
2. mitral valve disease
3. myocardial conduction abnormalities
4. decreased pulmonary compliance and reduced lung volume in patients with advanced thoracic kyphoscoliosis

Spinal cord injury: Following trauma, the routine of initially securing the head to a backboard with the neck in neutral position may be deleterious in the patient with kyphotic deformity related to AS[457]. AS may be suspected when the patient spontaneously holds their head in significant flexion[459], and in these cases the neck should be immobilized in that position[460]. When traction is used, the axis of traction (not the pin sites) often needs to be ventral to neutral and the use of minimal weight is recommended[457].

Subsequent treatment for SCI in AS is controversial: halo immobilization alone has been advocated by many, citing similar outcome and fewer complications. Others advocate early internal fixation because of cases of nonunion and progression of deficit while in the halo brace[457] and risk of skin

breakdown under the vest due to severe kyphosis. Neurologic deficit related to cord or root compression is an indication for decompressive laminectomy and fusion[457].

Positioning for surgery may be difficult due to the immobile kyphotic spine. Anterior approaches are difficult due to extensive bridging osteophytes, and the screws for anterior plates may not hold well in the osteoporotic VBs. Posterior cervical lateral mass plating (*see page 179*) is advocated for most.

Kyphotic deformity: Severe flexion deformity may be treated by spinal osteotomy[453].

18.10. Ossification of the posterior longitudinal ligament (OPLL)

Key concepts:

- fibrosis followed by calcification and then ossification of the posterior longitudinal ligament. The process may involve the dura
- more common in Asian population
- most patients have only mild subjective complaints
- 50% of patients have impaired glucose tolerance, respiratory compromise may result from ossification of the costotransverse and costovertebral ligaments
- surgery is best for moderate neuro involvement (Nurick grade 3 & 4)

The age of patients with OPLL ranges from 32-81 years (mean = 53), with a slight male predominance. The prevalence increases with age. Duration of symptoms averages ≈ 13 months. It is more prevalent in the Japanese population (2-3.5%)[461, 462].

Pathophysiology

The pathologic basis of OPLL is unknown, but there is an increased incidence of ankylosing hyperostosis which suggests a hereditary basis.

OPLL begins with hypervascular fibrosis in the PLL which is followed by focal areas of calcification, proliferation of periosteal cartilaginous cells and finally ossification[463].

The process frequently extends into the dura. Eventually active bone marrow production may occur. The process progresses at varying rates among patients, with an average annual growth rate of 0.67 mm in the AP direction and 4.1 mm longitudinally[464].

When hypertrophied or ossified, the posterior longitudinal ligament may cause myelopathy (due to direct spinal cord compression, or ischemia) and/or radiculopathy (by nerve root compression or stretching).

Changes within the spinal cord involve the postero-lateral gray matter more than white matter, suggesting an ischemic basis for the neurologic involvement.

Distribution

Average involvement: 2.7-4 levels. Frequency of involvement:

1. cervical: 70-75% of cases of OPLL. Typically begins at C3-4 and proceeds distally, often involving C4-5 and C5-6 but usually sparing C6-7
2. thoracic: 15-20% (usually upper, ≈ T4-6)
3. lumbar: 10-15% (also usually upper, ≈ L1-3)

Pathologic classification[465]

1. segmental: confined to space behind vertebral bodies, does not cross disc spaces
2. continuous: extends from VB to VB, spanning disc space(s)
3. mixed: combines elements of both of the above with skip areas
4. other variants: includes a rare type of OPLL that is contiguous with the endplates and is confined to the disc space (involves focal hypertrophy of the PLL with punctate calcification)

Clinical

Most patients are asymptomatic, or have only mild subjective complaints. This is probably explained by the protective effect of the fusion resulting from OPLL and the very gradual compression.

Natural history: 17% of patients without myelopathy developed myelopathy in one study[466] over 1.6 years mean follow-up. Statistically, the myelopathy-free rate in patients without initially presenting with myelopathy was 71% after 30 years[466].

Evaluation

Plain x-rays

Often fail to demonstrate OPLL.

MRI

OPLL appears as a hypointense area and is difficult to appreciate until it reaches ≈ 5 mm thickness. On T1WI it blends in with the hypointensity of the ventral subarachnoid space; on T2WI it remains hypointense while the CSF becomes bright. Sagittal images may be very helpful in providing an overview of the extent of involvement, and T2WI may demonstrate intrinsic spinal cord abnormalities which may be associated with a worse outcome.

Myelography/CT

Myelography with post-myelographic CT (especially with 3D reconstructions) is probably best at demonstrating and accurately diagnosing OPLL.

TREATMENT

Treatment decisions

Based on clinical grade[465] as follows:

- Class I: radiographic evidence without clinical signs or symptoms. Most patients with OPLL are asymptomatic[462]. Conservative management unless severe
- Class II: patients with myelopathy or radiculopathy. Minimal or stable deficit may be followed expectantly. Significant deficit or evidence of progression warrants surgical intervention
- Class IIIA: moderate to severe myelopathy. Usually requires surgical intervention
- Class IIIB: severe to complete quadriplegia. Surgery is considered for incomplete quadriplegics showing progressive slow worsening. Rapid deterioration or complete quadriplegia, advanced age or poor medical condition are all associated with worse outcome

In moderate grade patients (Nurick grades 3 & 4363, *see Table 18-35*), surgery provided a statistically significant reduction in deterioration. There was no difference between surgery and conservative treatment in mild grade (Nurick

1 or 2), and surgery was ineffective in severe grade (Nurick 5)[466].

Pre-op assessment

Appropriate cardiorespiratory assessment should be made knowing that:

- respiratory compromise may result from ossification of the costotransverse and costovertebral ligaments
- 50% of patients have impaired glucose tolerance with the attendant risks associated with diabetes

Table 18-35 Nurick grade of disability from cervical spondylosis[363]

Grade	Description
0	signs or symptoms of root involvement without myelopathy
1	myelopathy, but no difficulty in walking
2	slight difficulty in walking, able to work
3	difficulty in walking but not needing assistance, unable to work full-time
4	able to walk only with assistance or walker
5	chairbound or bedridden

Technical considerations for surgery

Severe OPLL increases the risk of spinal cord injury during neck positioning for intubation, and strong consideration should be given to awake nasotracheal intubation.

An anterior approach is generally favored, although laminectomy may be acceptable. SSEP monitoring has been recommended by some[463]. Distraction should be avoided until the spinal cord has been decompressed from the OPLL.

Some authors advocate complete removal of bone from the dura, while others feel it is permissible to leave a thin rim of bone adherent to the dura. Care must be taken in removing bone because it tends to blend imperceptibly with dura and the next thing one may see is bare spinal cord.

Depending on the distance of vertical involvement, vertebral corpectomy with strut grafting may be required. Internal plate fixation is often used as an adjunct. Post-operative immobilization for at least 3 months is employed with rigid collars for single level ACDF or 1-2 level corpectomies, or halo-vest traction for corpectomies > 2 levels.

Results with surgery

The incidence of pseudarthrosis after vertebral corpectomy and strut graft ranges from 5-10% and increases with the number of levels fused.

In one series there was a 10% incidence of transient worsening of neurologic function following anterior surgery[464] which may have been related to distraction.

The risk of dural tear with CSF leak following an anterior approach depends on the aggressiveness with which bone is removed from the dura, and ranges ≈ 16-25%.

Other risks of anterior approaches (see *ACDF complications*, page 465) also pertain.

18.11. Ossification of the anterior longitudinal ligament (OALL)

OALL of the cervical spine and/or hypertrophic anterior cervical osteophytes may produce dramatic radiographic findings and minimal clinical symptoms. Distinct from Forestier's disease (*see below*). Cervical involvement may produce dysphagia[467].

18.12. Diffuse idiopathic skeletal hyperostosis

Key concepts:

> • usually asymptomatic, but may present with globus
> • W/U: ✔ speech therapy consult for dysphagia evaluation (usually includes ✔ modified barium swallow), ✔ CT of cervical spine, ✔ ± digital video esophagoscopy

AKA "**DISH**", AKA spondylitis ossificans ligamentosa, AKA ankylosing hyperostosis, among others. A condition characterized by flowing osteophytic formation of the spine in the absence of degenerative, traumatic, or post-infectious changes. Affects Caucasians and males more commonly, and usually seen in patients in their mid 60s.

97% of cases occur in the thoracic spine, also in the lumbar spine in 90%, cervical spine in 78%, and all three segments in 70%. Sacroiliac joints are spared (unlike anky-losing spondylitis **(AS)**, *see page 502*). As with AS, unfused levels may be very unstable.

Usually does not produce clinical symptoms. Patients may have early morning stiffness and mild limitations of activities. Cervical involvement may present with dysphagia or **globus** (globus pharyngis: a sensation of a lump in the throat) due to compression of the esophagus between the osteophytes and the rigid laryngeal structures[468] (part of Forestier's disease[469]).

Plain x-rays and CT scan demonstrates the pathology. In cases of dysphagia, evaluation should include speech therapy consult for dysphagia evaluation, modified barium swallow to help localize the site of obstruction, and DVE (digital video esophagoscopy) to rule-out intrinsic esophageal disease.

Treatment: Cases that do not respond satisfactorily to dietary modifications in patients who are losing weight or are having recurrent episodes of choking or pneumonia should be considered for surgery. An anterior cervical approach, and utilization of a high-speed drill with careful protection of soft-tissue structures (esophagus, carotid sheath) without need for discectomy nor spine stabilization has been recommended[468]. Patients need to be made aware that post-op they are likely to be worse initially (from manipulation of esophagus and possibly disruption of some of the autonomic innervation of the esophagus) and will probably need a gastrostomy feeding tube. By 1 year post-op there may be some improvement.

18.13. Scheuermann's kyphosis

AKA Scheuermann juvenile kyphosis or kyphoscoliosis AKA Scheuermann disease AKA juvenile osteochondrosis of the spine.

Definition: anterior wedging of at least 5° of ≥ 3 adjacent thoracic vertebral bodies.

Other findings include: Schmorl nodes (*see page 455*) and endplate narrowing.

Presentation

Adolescents: often present as a result of the cosmetic deformity associated

with progressive kyphosis which may be mistaken for “slouching”.

Adults: often present with pain.

Radiographic findings

Anterior wedge deformities at multiple levels. End plate irregularities and Schmorl’s nodes.

Treatment

Bracing may be used in adolescents.

Adults presenting with pain often respond to nonsurgical treatment including: physical therapy and NSAIDs.

Surgical indications: refractory pain, progressive kyphosis, or neurologic deficit.

18.14. Spinal vascular malformations

Often also referred to by the term spinal AVMs which technically refers to a subset of spinal vascular malformations **(SVMs)**. Incidence of SVM is about 4% of primary intraspinal masses. 80% occur between age 20 and 60 years[470] (p 1850-3).

Classification

Classification is evolving (see review by Black[471]). 3 current era systems:

The “American/English/French Connection[A] classification

References for classification: include[472-479]

- Type I: **dural AVM** AKA AV-fistula **(AVF)**. The most common type (80%) of SVM in the adult[480]. Fed by radicular artery which forms an AV shunt (fistula) at the dural root sleeve (located in the intervertebral foramen)[477], drains into an engorged spinal vein on posterior cord. Usually in lumbar or lower thoracic spine. Slow flow. High pressure in draining vein may cause venous congestion of the cord. Cord involvement may be distant to the

fistula. Symptoms: LBP and progressive myeloradiculopathy or cauda equina syndrome (due to venous congestion) with urinary retention usually in middle-aged patients, 90% males. Up to 35% have pain. 15-20% are associated with other AVMs (cutaneous or other). Rarely bleed

- Type IA: single arterial feeder
- Type IB: two or more arterial feeders

• intradural AVMs (high flow): 75% present with acute onset of symptoms, usually from hemorrhage (SAH or intramedullary)

- Type II: AKA **spinal glomus AVM**. Intramedullary. True AVM of the spinal cord. 15-20% of all SVMs. Compact nidus fed by medullary arteries with the AV shunt contained at least partially within the spinal cord or pia. May be associated with feeding artery aneurysms. Worse prognosis than dural AVM[477]. Fed by 1, or at most 2-3 feeders 80% of the time
- Type III: AKA **juvenile spinal AVM**. Essentially an enlarged glomus AVM which occupies the entire cross-section of the cord and invades the vertebral body which may cause scoliosis
- Type IV[476]: intradural **perimedullary AVM** (also called arteriovenous *fistulae* - **(AVF)**). Direct fistula between artery supplying spinal cord (usually anterior spinal artery, often artery of Adamkiewicz) and draining veins. Typically occur in younger patients than Type I, and may present catastrophically with hemorrhage into the subarachnoid space[481]. *Table 18-36* shows the 3 subtypes[478].

• miscellaneous spinal vascular lesions:

- spinal cord cavernomas
- spinal cord venous angiomas: extremely rare. Difficult to visualize angiographically
- vertebral body hemangiomas (*see* *page 738*)

A. this descriptive label was coined by Black[471]

Table 18-36 Merland's subclassification of Type IV (perimedullary) AV fistulas*

Sub-type	Arterial Supply	AVF	Venous Drainage
I	single (thin ASA)	single, small	slowly ascending perimedullary venous system
II	multiple (dilated ASA & PSA)	multiple, medium	
III		single, giant	giant venous ectasia, rapid metameric venous drainage

* AVF = arteriovenous fistula; ASA = anterior spinal artery; PSA = posterior spinal artery

Hôpital Bicêtre classification[482]

A. AVMs
B. fistulae: micro- or macrofistulae
C. genetic classification of spinal cord AV shunts
  a. genetic hereditary lesions: macrofistulae and hereditary hemorrhagic telangiectasias
  b. genetic nonhereditary lesions: multiple lesions with metameric or myelomeric associations
  c. single lesions: incomplete associations of categories a or b

Spetzler, et al. classification[483]

(this system reincorporated vascular spinal neoplasms)

1. neoplastic vascular lesions
   A. hemangioblastoma
   B. cavernous malformation
2. spinal aneurysms (rare)
3. arteriovenous lesions
   A. AVFs
      • extradural
      • intradural: dorsal or ventral
   B. AVMs
      • extradural-intradural
      • intradural
      • intramedullary
      • intramedullary-extramedullary
      • conus medullaris

Presentation

85% present as progressive neuro deficit (back pain associated with progressive sensory loss and LE weakness over months to years). Yet, SVMs account for < 5% of lesions presenting as spinal cord "tumors". 10-20% of SVMs present as sudden onset of myelopathy usually in patients < 30 yrs age[484, 485], secondary to hemorrhage (causing SAH, hematomyelia, epidural hematoma, or watershed infarction). **Coup de poignard of Michon** = sudden excruciating back pain with SAH (clinical evidence of SVM).

Foix-Alajouanine syndrome (subacute necrotic myelopathy): acute or subacute neurologic deterioration in a patient with a SVM without evidence of hemorrhage. Presents as spastic → flaccid paraplegia, with ascending sensory level and loss of sphincter control. Initially thought to be due to spontaneous thrombosis of the AVM causing sub-acute necrotizing myelopathy[486] which would be irreversible. However, more recent evidence suggests that the myelopathy may be due to venous hypertension with secondary ischemia, and there may be improvement with treatment[487].

Clinical

Auscultation over spine reveals a bruit in 2-3% of cases. Cutaneous angioma over back is present in 3-25%; valsalva maneuver may enhance the redness of the angioma[485].

Evaluation

Spinal angiography: necessary for treatment planning. Best performed at centers that do this study regularly. For Type I dural AVMs, angiography must encompass all dural feeders of the neuraxis, which includes:

1. ICAs: because of the artery of Bernasconi & Cassinari (*see page 99*)
2. every radicular artery including the artery of Adamkiewicz (*see page 96*)
3. internal iliac arteries: for sacral feeders

MRI: detects some SVMs with greater sensitivity and safety than angiography[488], but is inadequate for treatment planning. 82% show extramedullary flow voids. Variable degree of cord enhancement (from venous congestion or venous infarction). Negative MRI does not rule out diagnosis.

Myelography: classically shows serpiginous intradural filling defects. Generally superseded by MRI. If done, patient should be imaged prone and supine (to avoid missing a dorsal AVM) ✖ Risk of bleeding from puncture of a dilated artery/vein with myelography needle.

Treatment

Type I (dural AVMs): usually require treatment. Usually amenable to endovascular techniques using glue, in which case the proximal vein must be taken as well. If you don't completely eliminate a dural fistula (spinal or intracranial) it will come back!

Type II (spinal glomus AVMs): may be amenable to interventional neuroradiologic procedures including embolization[489], especially type IIA (single feeder). However recurrence may be higher with endovascular treatment than surgery, and surgery is often preferred for Type IIB (≥ 2 feeders).

Surgical strategy: similar to intracranial AVMs except that the parenchyma cannot be retracted, bleeding is rarely life threatening, and arteries of passage must be preserved to avoid devastating deficits. Intraoperative ICG angio is often helpful. The nidus is compact, and the hemosiderin ring around the nidus on MRI often represents a plane that can be exploited.

Type III (juvenile spinal AVMS): the natural history is probably better than the prognosis with any type of treatment.

Type IV (perimedullary fistulae): *see Table 18-37* for suggested management[479].

Table 18-37 Suggested management for Type IV arteriovenous fistulae[479]

Subtype	Diagnosis	Embolization	Surgery
Subtype I	difficult; ? reliability of MRI*; tomomyelography; angiotomomyelography	difficult	easy on filum terminale; difficult on conus medullaris
Subtype II	easy: MRI or myelography	incomplete occlusion	on posterolateral AVFs
Subtype III		effective	difficult, dangerous

* due to inaccuracy, do not delay angiogram to get MRA, etc.

18.15. Spinal meningeal cysts

Spinal meningeal cysts **(SMC)**: diverticula of the meningeal sac, nerve root sheath or arachnoid. May have familial tendency.

Terminology in literature is confusing. One classification system is shown in *Table 18-38*. Previously AKA Tarlov's perineural cysts, spinal arachnoid cysts, and extradural diverticula, pouches or cysts. Only congenital lesions are considered here.

- Type I SMCs above the sacrum usually have a pedicle adjacent to entrance

of dorsal nerve root

- Type II SMCs: formerly called Tarlov's cysts and were differentiated from nerve root diverticula because the former were defined as communicating with subarachnoid space, and the latter not. However, intrathecal contrast CT **(ICCT)** shows both communicate. Often multiple, occur on dorsal roots anywhere, but are most prominent and symptomatic in sacrum
- Type III SMCs: may also be multiple and asymptomatic. More common along posterior subarachnoid space. Attributed to proliferation of arachnoid trabeculae

Table 18-38 Types of spinal meningeal cysts[490]

Type	Description
Type I	extradural meningeal cysts without spinal nerve root fibers
IA	"extradural meningeal/arachnoid cyst"
IB	(occult) "sacral meningocele"
Type II	extradural meningeal cysts with spinal nerve root fibers ("Tarlov's perineural cyst", "spinal nerve root diverticulum")
Type III	spinal intradural meningeal cysts ("intradural arachnoid cyst")

Presentation

May be asymptomatic (i.e. incidental finding). May cause radiculopathy by pressure on adjacent nerve root (may or may not cause symptoms of nerve root from which it actually arises). Symptom complex depends on size of SMC, and proximity to spinal cord and nerve roots.

- Type I SMCs: in thoracic and cervical region, may present with acute myelopathy (spasticity and sensory level); lumbar region → LBP and radiculopathy; sacral region → sphincter disturbance
- Type II SMCs: often asymptomatic, but sacral lesions may → sciatica and/or sphincter disturbance
- Type III SMCs: may also be multiple and asymptomatic; more common along posterior subarachnoid space

Evaluation

MRI to identify the mass, then water-soluble ICCT scan to evaluate communication of cyst with subarachnoid space.

- Type II SMCs: all 18 cases had bony erosion (demonstrated by canal widening,

pedicle erosion, foraminal enlargement, or vertebral body scalloping)
- Type III SMCs: may also cause bony erosion; appear on myelogram as intradural defect, may not appear on ICCT if they communicate with subarachnoid space which causes them to blend with adjacent subarachnoid space

Treatment
- Type I SMCs: close ostium between cyst and subarachnoid space. Above sacrum, can usually be dissected from dura; occasionally fibrous adhesions prevent this
- Type II SMCs: no pedicle, thus either partially resect and oversew cyst wall, or excise cyst and involved nerve root. Simple aspiration is not recommended
- Type III SMCs: excise completely unless dense fibrous adhesions prevent this, in which case marsupialize cyst. Tend to recur if incompletely excised

18.16. Syringomyelia

Key concepts:

> - AKA syrinx. Cystic cavitation of the spinal cord
> - 70% are associated with Chiari I malformation, 10% with basilar invagination. May also be posttraumatic or associated with tumor, infection…
> - symptoms: progressive neurologic deterioration over months to years, usually affecting UE first
> - diameter > 5 mm + associated edema predict a more rapid deterioration
> - preferred treatment is directed at correcting the causative pathophysiology

AKA **syrinx**. Cystic cavitation of the spinal cord. Other terms not precisely defined include: **hydrosyringomyelia**, communicating or noncommunicating syringomyelia.

Syringobulbia: Rostral extension into brainstem (usually medulla). May present with (bilateral) peri-oral tingling and numbness, due to compression of the spinal trigeminal tracts as the fibers decussate.

DISTINGUISHING FROM SIMILAR ENTITIES

1. tumor cyst:
   A. especially with intramedullary spinal cord gliomas. Tumors may secrete fluid, or may cause microcysts that eventually coalesce. Most (but not all) intramedullary tumors will enhance with IV contrast on MRI
   B. tumor cyst fluid is usually highly proteinaceous, syrinx fluid usually has the same MRI characteristics as CSF (NB: true syrinx can occur with tumor)
2. central spinal canal
   A. residual **central spinal canal**: the central canal is present within the spinal cord at birth and normally gradually involutes with age[491]. Persistence of the canal is a normal variant. Characteristic imaging features:
      1. linear or fusiform on sagittal MRI
      2. $\leq$ 2-4 mm in maximal width
      3. may be singular, or there may be several discontinuous regions in the rostral-caudal direction
      4. perfectly round in cross-section and centrally located on axial MRI
      5. if IV contrast is given, there should be no enhancement
   B. simple dilatation of the central canal with ependymal cell lining has some-times been called **hydromyelia**, but this usage is ambiguous

ETIOLOGIES

1. primary syringomyelia: this term is used differently by different authors[492]. Herein, refers to syrinx in the absence of identifiable cause
2. secondary syringomyelia: Most cases are thought to be secondary to partial obstruction of the spinal subarachnoid space[492]. Unanswered question: Why then do patients with varying degrees of degenerative cervical spinal stenosis generally not get syringomyelia?
   A. Chiari I malformation: the most common cause of syrinx (*see page 233*)
   B. postinflammatory
      1. postinfectious
         a. granulomatous meningitides (TB and fungal)
         b. postoperative meningitis, especially after intradural procedure
      2. chemical or other sterile inflammations

a. rarely after SAH
b. after myelography: especially with older agents no longer in use (ophendylate (Pantopaque®))

C. posttraumatic: also *see below*
  1. with severe posttraumatic kyphotic deformity: e.g. with retropulsed bone, scarring…
  2. arachnoid scarring without recognized trauma
  3. severe injury to spinal cord and/or its coverings. Blood may be a contributing factor

  ✖ the older concept of syrinx developing as a coalescence of foci of traumatic hematomyelia has not been borne out

D. postsurgical: has been identified many years after uncomplicated intradural neoplasm removal (e.g. neurofibromas)

E. basilar arachnoiditis:
  1. idiopathic
  2. postinfectious: *see above*

F. basilar impression (with constriction of the foramen magnum, *page 138*)

G. associated with spinal tumors: this is distinct from a tumor cyst

H. associated with disc protrusion:

I. cerebellar ectopia

J. Dandy Walker syndrome

EPIDEMIOLOGY[493]

Prevalence of non-posttraumatic syringomyelia: 8.4 cases/100,000 population. Usually presents between ages 20-50.

Associated clinical syndromes are shown in *Table 18-39*.

Table 18-39 Conditions associated with syringomyelia

Condition	%*
Chiari type 1 malformation	70
basilar invagination	10
intramedullary spinal cord tumors	4

* percent of cases of syringomyelia

PATHOPHYSIOLOGY

Major theories of formation of the cyst:

- hydrodynamic ("water-hammer") theory of Gardner: systolic pulsations are transmitted with each heartbeat from the intracranial cavity to the central canal. Has been essentially disproven using MRI[494]
- Williams' ("craniospinal dissociation") theory: maneuvers that raise CSF pressure (valsalva, coughing…) cause "hydrodissection" through the spinal cord tissue. May be more common in noncommunicating syringomyelia
- Heiss-Oldfield theory: occlusion at the foramen magnum causes CSF pulsations during cardiac systole to be transmitted through the Virchow-Robin spaces which increases the extracellular fluid which coalesce to form a syrinx[493] (i.e. through the cord parenchyma)

CLINICAL

Presentation: highly variable. Usually progresses over months to years, with a more rapid deterioration early that gradually slows[493]. Initially, pain, weakness, atrophy and loss of pain & temperature sensation in the upper extremities (with cervical syrinx) is common. Myelopathy that progresses slowly over years ensues.

Characteristic syndrome

(nonspecific for intramedullary spinal cord pathology):

- sensory loss (similar to central cord syndrome) with a suspended ("cape") dissociated sensory loss (loss of pain and temperature sensation with preserved touch and joint position sense → painless ulcerations from unperceived injuries and/or burns)
- **pain**: commonly cervical and occipital. Dysesthetic pain often occurs in the distribution of the sensory loss[493]
- **weakness**: lower motor neuron weakness of the hand and arm
- painless (neurogenic) arthropathies (**Charcot's joints**) especially in the shoulder & neck due to loss of pain & temperature sensation: seen in < 5%

EVALUATION

Prior to the CT/MRI era, diagnosis relied on myelography or on autopsy.

MRI: defines anatomy in sagittal as well as axial plane. Test of choice. Cervical & thoracic spine and brain MRI (without & with contrast, to include craniocervical junction) should be obtained. Syringomyelic cavities may be complex, with noncommunicating channels (more common with posttraumatic

syrinx).

CT: low attenuation area within cord seen on either plain CT or myelogram/CT (with water soluble contrast).

Myelogram: rarely used alone (usually performed in conjunction with CT). When used alone: often normal (false negative), some → complete block at level of syrinx; iodine contrast studies may show fusiform widening of spinal cord, whereas air contrast studies may show collapse of the cord[495]. Dye may slowly leach into the cyst.

EMG: no characteristic findings, but may be useful to R/O other conditions that may be responsible for symptoms (e.g. peripheral neuropathy causing paresthesias).

MANAGEMENT

For an incidentally discovered syrinx (i.e. asymptomatic and no neurologic deficit) with no identified etiology, if the size remains stable over 2-3 years of observation, F/U studies at 2-3 year intervals can be done if there are no changes in symptoms.

SURGICAL TREATMENT

Intervention is considered for symptomatic lesions (not all are symptomatic). If an underlying cause cannot be determined, it may be very difficult to treat a very small syrinx directly (however, these are unlikely to be causing reversible symptoms).

Options include:

1. current philosophy is to treat the underlying pathophysiology (and to use syrinx draining procedures as second choice when this is not feasible)
   A. posterior decompression: procedure of choice when posterior anomalies (e.g. Chiari malformation) are present
   B. decompression if a different site of compression is identified
2. shunts:
   A. disadvantages:
      1. complication rate: 16%
      2. clinical stabilization rate: 54% at 10 yrs
      3. may produce traction on spinal cord with potential for further injury
      4. prone to obstruction: 50% at 4 years
      5. does not correct underlying pathophysiology and so syrinx may

recur

B. indications: cases of diffuse arachnoiditis (e.g. following tuberculous or chemical meningitis) where the obstruction extends over many levels, and syrinx diameter > 3-4 mm

C. **K** or **T** tube drainage. Choice of distal sites includes:

1. peritoneum[496] (difficult in cervical region)
2. pleural cavity
3. subarachnoid space (e.g. Heyer-Schulte-Pudenz system): requires normal CSF flow in subarachnoid space, therefore cannot use in arachnoiditis

3. percutaneous aspiration of the cyst[497] (may be used repeatedly)
4. ✖ no longer recommended:
   A. plugging the obex with muscle, teflon or other material
   B. opening the subarachnoid space & removing inferior tonsils
   C. syringostomy: usually fails to remain patent, therefore using a stent or a shunt (syringosubarachnoid or syringoperitoneal) is recommended

Technical considerations:

1. intraoperative ultrasound may be helpful for:
   A. localizing the cyst
   B. assessing for septations (to avoid shunting only part of cyst)
2. if Chiari malformation is not present, consider syringosubarachnoid shunt as the initial procedure. If this fails, then syringoperitoneal shunt may be inserted
3. Rhoton suggests performing the myelotomy in the dorsal root entry zone (DREZ), between the lateral and posterior columns (instead of the midline as with a tumor) because this is consistently the thinnest part and there is usually already an upper extremity proprioceptive deficit from the syrinx[123 (p 1317)]. There is ≈ 10% incidence of posterior column dysfunction with shunting
4. with syringosubarachnoid shunts, be sure the distal shunt tip is subarachnoid (and not just subdural) or else it will not function
5. with syringopleural shunt, the pleural opening can be made posteriorly, adjacent to one of the ribs as described for ventriculopleural shunt (*see page 210*)

OUTCOME

Assessing treatment results is difficult due to rarity of the condition, variability of natural history (which may arrest spontaneously), and too short follow-up[498]. Enthusiasm for direct treatment (shunts, fenestration…) is low among neurosurgeons because of the perceived poor response and risk of iatrogenic neurologic worsening.

18.16.1. Posttraumatic syringomyelia

Posttraumatic syringomyelia **(PTSx)** may follow significant spinal trauma (with or without clinical spinal cord injury). Includes penetrating injury or non-penetrating "violent" trauma to the spinal cord (injuries such as post-spinal anesthesia or following thoracic disc herniation are not included).

EPIDEMIOLOGY

Often a late presentation following spinal cord injury, therefore incidence is higher in series with longer follow-up. Incidence increasing with increasing survival following spinal cord injury and with increasing use of MRI. Range: ≈ 0.3-3% of cord injured patients (*see Table 18-40*).

In a large number of patients followed via multicenter cooperative data bank, there were fewer cases of syrinx following cervical injuries than following thoracic injuries[500] (may be artifactual since patients with lower lesions may be more aware of ascending levels).

Table 18-40 Incidence of posttraumatic syringomyelia

Type of injury	No./risk*	Incidence
all spinal cord injury patients	30/951	3.2%
complete quadriplegics	14/177	7.9%
incomplete quadriplegics	4/181	4.5%
complete paraplegics	4/282	1.7%
incomplete paraplegics	4/181	2.2%

* number occurring over number at risk in 951 patients followed for 11 years[499]

Latency following spinal cord injury:

- latency to symptoms: 3 mos to 34 yrs (mean 9 yrs) (earlier in complete cord lesions than incomplete: mean 7.5 vs. 9.9 yrs)
- latency to diagnosis: up to 12 yrs (mean 2.8 yrs) after onset of new symptoms

CLINICAL

The presentation of patients with PTSx is shown in *Table 18-41*. The late appearance of upper extremity symptoms in a paraplegic patient should raise a high index of suspicion of posttraumatic syringomyelia[502].

Hyperhidrosis may be the only feature of descending syringomyelia in patients with complete cord lesions[503]. For the differential diagnosis, see *Delayed deterioration following spinal cord injuries*, page 1000.

EVALUATION

One end of the cavity is often found at a site of spinal column fracture or abnormal angulation.

MANAGEMENT

Many authors advocate early surgical drainage of cyst as a means of reducing increased delayed deficit[504]. Some authors feel that aside from disturbing sensory symptoms, that motor loss was infrequent and therefore conservative management is indicated in most cases[505].

MEDICAL

Managed non-surgically: 31% stable, 68% progressed over yrs (longer F/U in latter).

SURGICAL

There is probably no benefit in operating on a patient with a small syrinx[499].

Surgical options:
As in *Communicating syringomyelia*, with the following differences:
- cord transection (cordectomy)[506]: an option in complete injuries only
- plugging the obex is probably not indicated (controversial in congenital syrinx)

Table 18-41 Presentation (in 30 SCI patients with syrinx[499])

Symptom	Initial	At time of diagnosis
pain*	57%	70%
numbness	27%	40%
increased motor deficit	23%	40%
increased spasticity	10%	23%
	3%	13%

increased sweating (hyperhidrosis)		
autonomic dysreflexia	3%	3%
no symptoms	7%	7%
Signs	**Frequency**	
ascending sensory level	93%	
depressed tendon reflexes	77%	
increased motor deficits	40%	

* pain is often quite severe, and unrelieved with analgesics[501]

OUTCOME

In 9 PTSx patients treated with syringosubarachnoid shunt[499]: pain relieved in all 9 (1 only slightly), motor recovery in 5/8, improved tendon reflex in 1/10. Some post-op complications in 9 patients included: 1 incomplete lesion became complete, 1 sensorimotor deterioration, transient pain in 3.

Most results are good for radicular symptoms, with dubious efficacy for autonomic symptoms or spasticity.

18.17. Spinal cord herniation (idiopathic)

Rare. Spinal cord herniates though a defect in the dura usually located anteriorly or anterolaterally between T2-8507. Bone erosion anterior to the dural defect may occasionally be seen. Frequently associated with a calcified disc fragment which theoretically may have gradually eroded through the dura.

Main DDx is with dorsal arachnoid cyst (*see page 1186*). Both result in increased subarachnoid space posterior to the cord, and a ventral kinking of the spinal cord. Contiguous CSF pulsation artifact on MRI can be seen with cord herniation, whereas an arachnoid cyst tends to interrupt this.

Commonly presents as an incomplete Brown-Séquard syndrome (with relative sparing of posterior columns). Symptoms may be due to distortion of the spinal cord, but vascular injury may also play a role.

Surgery

Requires a posterolateral or anterolateral approach to minimize spinal cord manipulation (*see page 471*). The dural defect is widened which usually results

in reduction of the spinal cord herniation. A sling of dural substitute can then be slid anterior to the cord to prevent reherniation.

18.18. Spinal epidural hematoma

Rare. Over 200 cases of varying etiology have been reported[508], although one third of recent cases have been associated with anticoagulation therapy[509]. NSAIDs may also be a risk factor[510]. Etiologies include:

1. traumatic: including following LP or epidural anesthesia[508, 511-513], fracture (*see below*), spinal surgery[162] or chiropractic manipulation[514]. Occurs predominantly in patient who is: anticoagulated[515], thrombocytopenic, or has bleeding diathesis or a vascular lesion
2. spontaneous[516]: rare. Etiologies: hemorrhage from spinal cord AVM (*see page 507*), from vertebral hemangioma (*see page 738*) or tumor

May occur at any level of the spine, however, thoracic is most common. Most often located posterior to spinal cord (except for hematomas following anterior cervical procedures), facilitating removal via laminectomy[509].

Traumatic spinal epidural hematoma (TSEH) associated with spine fracture:

In one series[517], among 74 trauma patients who underwent emergent spinal MRI, ≈ half of the patients with spine fractures also had TSEH. Treatment was based solely on the fracture, and the outcome in patients with neurologic deficits was no worse in the group with TSEH than in the group without.

Presentation

The clinical picture of spontaneous spinal epidural hematoma is fairly consistent but nonspecific. Usually starts with severe back pain with radicular component. It may occasionally follow minor straining, and is less commonly preceded by major straining or back trauma. Spinal neurologic deficits follow, usually progressing over hours, occasionally over days. Motor weakness may go unnoticed when patients are bedridden with pain.

Treatment

Recovery of neurologic deficit without surgery is rare[510], therefore optimal treatment is immediate decompressive laminectomy in those patients who can tolerate surgery[509]. In one series, most patients who recovered underwent decompression within 72 hrs of onset of symptoms[518]. In another, decompression within 6 hours was associated with better outcome[162].

High-risk patients: for medically high-risk patients (e.g. acute MI) on anticoagulation, surgical mortality and morbidity is extremely high, and this must be considered when making the decision of whether or not to operate. In patients not operated, anticoagulants should be stopped, and reversed if possible (see *Correction of coagulopathies or reversal of anticoagulants*, page 40). Consider use of high dose methylprednisolone to minimize cord injury (see *Methylprednisolone*, page 936 under spinal cord injury). Percutaneous needle aspiration may be a consideration in high-risk patients.

18.19. Spinal subdural hematoma

Rare. May be posttraumatic (including iatrogenic causes) or may occur spontaneously. Spinal subdural hematomas **(SSH)** that occur spontaneously or following lumbar puncture usually occur in patients with coagulopathies (primary or iatrogenic)[519].

Conservative treatment is possible in nontraumatic SSHs with minimal neurologic impairment[519].

18.20. Spinal epidural lipomatosis (SEL)

Hypertrophy of epidural fat, due to prolonged exogenous steroid therapy in most (75%) cases[520] (usually moderate to high dosage for years[521]), but may also be associated with: Cushing’s disease, Cushing’s syndrome, obesity[522], hypothyroidism or may be idiopathic[523]. Male:female = 3:1521.

Back pain usually precedes all other symptoms. Progressive LE weakness and sensory changes are common. Sphincter disturbance occurs but is rare. SEL is most common in the thoracic spine (≈ 60% of cases), the rest are in the lumbar spine (no cases reported in cervical spine).

Evaluation

CT: density of adipose tissue is extremely low (-80 to -120 Hounsfield units)[524] which distinguishes SEL from most other lesions (except lipoma).

MRI: signal follows fat (high signal on T1WI, intermediate on T2WI). Suggested diagnostic criteria: epidural adipose should be **> 7 mm** thick to be considered SEL[522, 525].

Treatment

In those patients who can be weaned off steroids and lose weight, surgery may be avoided in some cases[526]. If SEL is related to obesity, weight loss alone can be successful.

Surgery is indicated for symptomatic patients in whom the above interventions are unsuccessful or not feasible. An effort to normalize cortisol levels in those with endogenous hypercortisolism (Cushing's disease…) should be made before laminectomy is performed. Due to potential complications and slow growth of the tissue, the decision to operate surgery should made with caution.

Surgery usually consists of laminectomy with removal of adipose tissue. Occasionally repeat surgery is needed for reaccumulation of adipose tissue.

Outcome

Surgery usually results in significant improvement[525]. Idiopathic cases may fare better than those due to steroid excess. Cauda equina compression responds better than thoracic myelopathy.

Complications rates may be higher than expected in part due to medical comorbidities. Fessler et al.[527] reported 22% 1-year mortality.

18.21. Coccydynia

Pain and tenderness around the coccyx. A symptom, not a diagnosis. Typically, discomfort is experienced on sitting or on rising from sitting. More common in females, possibly due to a more prominent coccyx. The condition is unusual enough in males that in the absence of trauma, strong consideration should be given to an underlying condition.

Etiologies

For differential diagnosis, see *Acute low back pain*, page 1192. Better accepted etiologies include[528]:

1. local trauma (may be associated with fracture or dislocation):
   A. 25% of patients give a history of a fall
   B. 12% had repetitive trauma (rowing machine, prolonged bicycle riding…)
   C. 12% started with parturition
   D. 5% started following a surgical procedure (half of which were in the lithotomy position)
2. idiopathic: excluding traumatic cases, no etiology can be identified in most cases
3. neoplasms
   A. chordoma
   B. giant cell tumor
   C. intradural schwannoma
   D. perineural cyst
   E. intra-osseous lipoma
   F. carcinoma of the rectum
   G. sacral hemangioma[529]
   H. pelvic metastases (e.g. from prostate cancer)
4. prostatitis

Controversial etiologies include[528, 530]:

1. local pressure over a prominent coccyx
2. referred pain:
   A. spinal disease
      1. herniated lumbosacral disc
      2. cauda equina syndrome
      3. arachnoiditis
   B. pelvic/visceral disease
      1. pelvic inflammatory disease (PID)
      2. perirectal abscess
      3. perirectal fistula
      4. pilonidal cyst
3. inflammation of the various ligaments attached to the coccyx
4. neurosis or frank hysteria

Histological evaluation of the coccyx has not helped delineate the cause, even though avascular necrosis has been suggested[531].

Evaluation

Sacrococcygeal films are often performed to rule-out a bony destructive lesion. Often, the question of a fracture will be raised, and many times cannot be definitely ruled-in or out based on this study. There may or may not be any significance of such a fracture.

Nuclear bone scans were not helpful in 50 patients with coccydynia[528].

CT scan: no consistent findings.

Treatment

Most cases resolve within ≈ 3 months of **conservative management** consisting of NSAIDs, mild analgesics, and measures to reduce pressure on the coccyx (e.g. a rubber ring ("doughnut") sitting cushion, lumbar supports to maintain sitting lumbar lordosis to shift weight from coccyx to posterior thighs)[532].

Recurrence: Occurs in ≈ 20% of conservatively treated cases, usually within the first year. Repeat therapy was often successful in providing permanent relief. More aggressive treatment may be considered for refractory cases.

Management recommendations for refractory cases[528, 532]:

1. local injection: 60% respond to corticosteroid + local anesthetic (40 mg Depo-Medrol® in 10 cc of 0.25% bipuvicaine). Recommended as initial treatment; response should be achieved by 2 injections
2. manipulation of the coccyx: usually under general anesthesia. ≈ 85% successful when combined with local injection
3. ± physiotherapy (diathermy & ultrasound): found to be of benefit only in ≈ 16%
4. caudal epidural steroid injection
5. blockade or neurolysis (with chemicals or by cryoablation[533]) of the ganglion impar (AKA ganglion of Walther, the lowest ganglion of the paired paravertebral sympathetic chain, located just anterior to the sacrococcygeal junction): some success has been described with this technique (traditionally used for intractable sympathetic perineal pain of neoplastic etiology[534])

6. neurolytic techniques directed to S4, S5 and coccygeal nerves
7. coccygectomy (surgical removal of the mobile portion of the coccyx, followed by smoothening of the residual bony prominence on the sacrum): was required in ≈ 20% of patients in one series[528], with a reported success rate of 90%. However, many practitioners do not view this as a highly effective treatment and feel that great restraint should be used in considering this form of therapy

18.22. References

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NOTES

19. Functional neurosurgery

For functional neurosurgery related to pain, see *Pain procedures*, page 567.

19.1. Deep brain stimulation

This section covers issues related to deep brain stimulation **(DBS)** in general. For specific conditions, refer to that section. A variety of conditions may be treated including:

1. movement disorders
   A. Parkinson's disease: STN stimulation may be superior to best medical management[1, 2] because of similar efficacy to levodopa with fewer side effects (primarily dyskinesias) (*see below*)
   B. dystonia: *see page 536*
   C. tremor: *see page 545*
2. epilepsy: *see page 422*
3. pain: response is variable, typically only 25-60% respond (*see page 574*)
4. potential uses
   A. psychiatric disorders: mainly
      1. Tourette syndrome: thalamic & pallidal DBS (case reports[3, 4])
      2. obsessive compulsive disorders: anterior capsule and STN stimulation[5] and, recently, targets more posterior and rostral[6]
      3. depression: subgenual cingulate gyrus[7] and anterior capsule stimulation[8]
   B. obesity[9]
   C. drug addiction[10]
   D. hypertension (case report of lowering BP in a patient who was being treated for pain[11])

Typical targets used in functional brain surgery

Figure 19-1 depicts relationships of typical targets to other structures and

effects of DBS (or lesioning). This figure is intended for illustrative purposes only, and is not presented for purposes of performing surgical procedures.

19.2. Surgical treatment of Parkinson's disease

Historical background

An early procedure was ligation of the anterior choroidal artery. Due to variability in distribution, destruction often extended beyond the desired confines of the pallidum and the results were too unpredictable (*see page 1028*). Anterodorsal pallidotomy became an accepted procedure in the 1950's, but long-term improvement was mainly in rigidity, while tremor and bradykinesia did not improve[12]. The ventrolateral thalamus subsequently became the preferred target. Lesions there were most effective in diminishing tremor. In actuality, the tremor was often not the most debilitating symptom, particularly since it is a resting tremor at first (it may become more pervasive later). Bradykinesia and rigidity were frequently more problematic. Furthermore, the procedure only reduces tremor in the contralateral half of the body, and bilateral thalamotomies were not recommended due to an unacceptably high risk of post-op dysarthria and gait disturbance. Use of thalamotomy fell off dramatically in the late 1960's with the introduction of Ldopa[13].

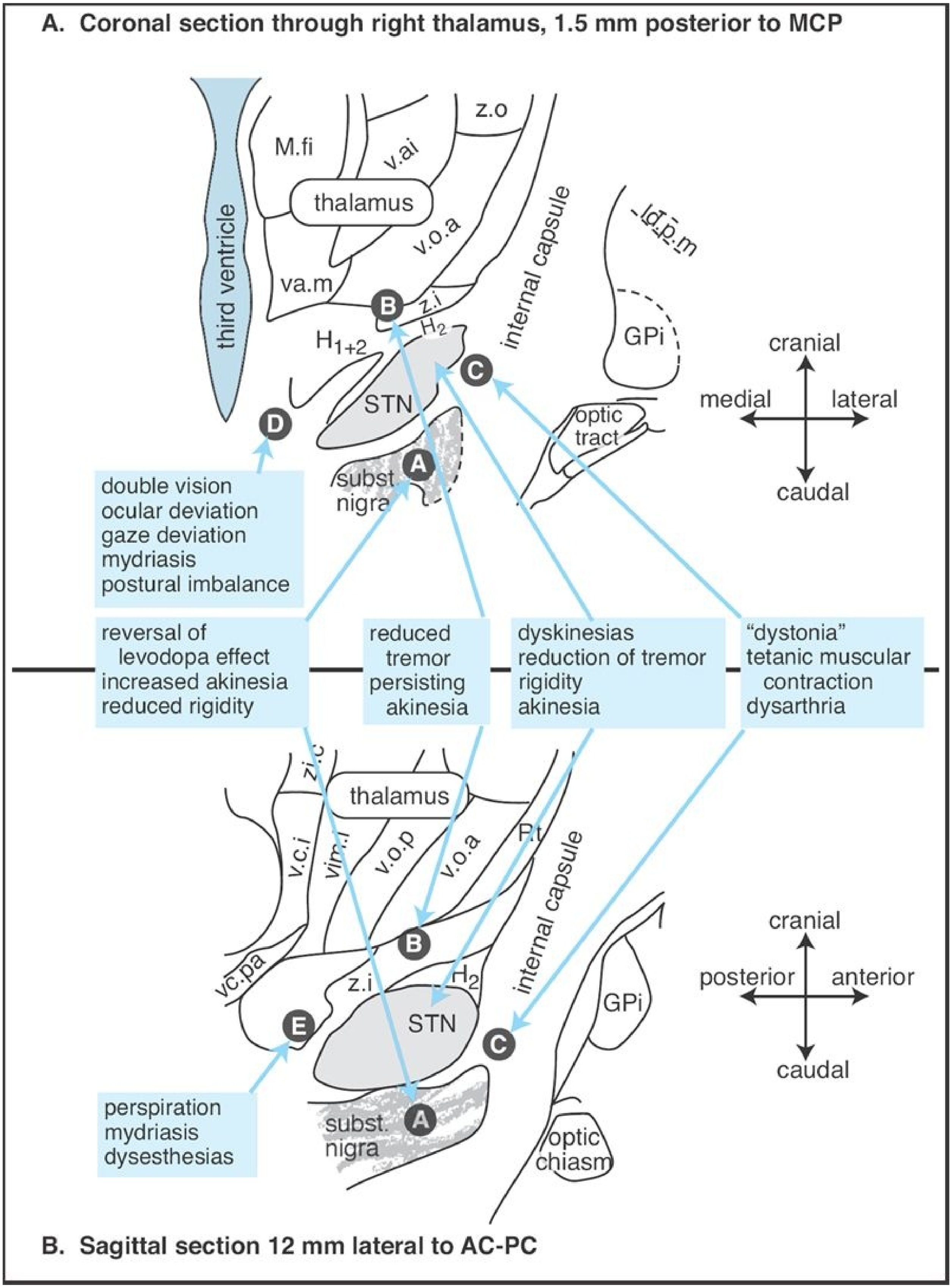
A. Coronal section through right thalamus, 1.5 mm posterior to MCP
z.o
M.fi
v.ai
thalamus
third ventricle
v.o.a
internal capsule
va.m
z.i
H2
H1+2
STN
GPi
optic tract
subst nigra
cranial
medial
lateral
caudal
double vision
ocular deviation
gaze deviation
mydriasis
postural imbalance
reversal of levodopa effect
increased akinesia
reduced rigidity
reduced tremor
persisting akinesia
dyskinesias
reduction of tremor
rigidity
akinesia
"dystonia"
tetanic muscular contraction
dysarthria
thalamus
v.c.i
vim.i
v.o.p
v.o.a
internal capsule
vc.pa
z.i
H2
STN
GPi
subst. nigra
optic chiasm
cranial
posterior
anterior
caudal
perspiration
mydriasis
dysesthesias
B. Sagittal section 12 mm lateral to AC-PC

Figure 19-1 Illustration of some targets for functional brain surgery Abbreviations: AC = anterior commissure, GPi = globus pallidus interna, H_1 = Forel's H_1 field, MCP = midcommissural point (halfway between AC & PC), PC = posterior commissure, STN = subthalamic nucleus, subst.nigr = substantia nigra, z.i = zona incerta

However, at some point most patients will experience problematic side effects and/or resistance to treatment with antiparkinsonian drugs. Tissue transplantation (e.g. with adrenal medullary tissue) appears to have only modest benefits (*see below*). Lesioning or stimulation techniques have therefore gained in popularity with renewed interest in the posteroventral pallidum as the target.

19.2.1. Tissue transplantation

Tissue transplantation for Parkinson's disease is generally limited to research centers. The present status of implantation of fetal dopaminergic brain cells into Parkinson's disease patients is that it may reduce the severity of the illness and increase the effectiveness of levodopa[14]. For ethical reasons, this procedure is rarely performed in the U.S.

Other transplanted tissues include cells from the patients own adrenal medulla. After initial enthusiastic results[15], later studies failed to corroborate the dramatic outcomes, and benefits appear to be modest[16-18].

A double-blinded, randomized, placebo-controlled trial[19] of 34 subjects with severe PD noted initial improvement at 6 and 9 months, but found no efficacy 2 years after fetal mesencephalic cell transplantation. Of note: immunosuppression was only used for six months. Further research is ongoing[20].

19.2.2. Ablative surgery & electrical stimulation

Ablative surgery is giving way to less destructive beep brain stimulation.

PALLIDOTOMY[21,22]

Pallidotomy may work by one of the following mechanisms: directly destroying portions of the internal segment of the globus pallidus internus **(GPi)**, interrupting pallid-ofugal pathways, or diminishing inputs to the medial pallidum (especially from the subthalamic nucleus) (see *Pathophysiology*, page 59). Although early methodologies included stereotactic radiosurgery[23], modern techniques (excluding very select cases) rely primarily on radiofrequency or cryoprobe lesioning after confirming target location by electrical stimulation.

Electrical stimulation: Deep brain stimulation **(DBS)** in the area of the GPi[24] and subthalamic nucleus **(STN)** can also relieve parkinsonian symptoms[25] without irreversibly destroying tissue. A randomized study showed similar efficacy between thalamotomy and DBS, but fewer side-effects with DBS[26]. A more recent target of interest for DBS is the pedunculopontine nucleus **(PPN)**.

Indications

1. patients refractory to medical therapy (including multiple agents). However, some investigators feel the response to surgery might be better if done early
2. primary indication (based on an opinion survey[27]): patients with levodopa-induced dyskinesias (especially those with associated painful muscle spasms). Initial results indicate that these are very responsive to pallidotomy
3. gait and postural instability[28] as well as falls and freezing[A29] may respond to DBS of the pedunculopontine nucleus **(PPN)**
4. patients primarily with rigidity or bradykinesia (unilateral or bilateral), on-off fluctuations or dystonia. Tremor may be present, but if it is the predominant symptom, then using the ventralis intermedius **(VIM)** nucleus of the thalamus as the target (for ablation (thalamotomy) or stimulation)[30] is a better procedure. VIM stimulation is also used to treat essential tremor[31]

A. non-human primate data

Contraindications

1. patients with significant dementia: further cognitive impairment has been noted primarily in patients with cognitive deficits prior to treatment
2. patients with risk of intracerebral hemorrhage: those with coagulopathy, poorly controlled hypertension, those on anti-platelet drugs that cannot be withheld (may consider stereotactic radiosurgery lesions for these rare patients)
3. patients with ipsilateral hemianopsia: due to the risk of post-op contralateral hemianopsia from optic tract injury which would make the

patient blind
4. age ≥ 85 yrs
5. patients with secondary Parkinsonism (*see page 60* for more details) i.e. <u>not</u> idiopathic Parkinson's disease: respond poorly, presumably due to different patho-physiology. Look for:
   A. signs of autonomic nervous system dysfunction (suggests Shy-Drager)
   B. EOM abnormalities (may occur in progressive supranuclear palsy **(PSNP)**)
   C. long-tract signs
   D. cerebellar findings (as in olivo-ponto-cerebellar atrophy **(OPCA)**)
   E. failure to improve with levodopa
   F. MRI: lacunar infarcts in basal ganglia (as in arteriosclerotic Parkinsonism), or tumor in region of substantia nigra
   G. PET scanning (if available): decreased striatal metabolism detected by deoxyglucose PET scan (suggests striato-nigral degeneration **(SND)**)

TECHNIQUE

Antiparkinsonian medications are withheld the morning of the procedure to bring out symptoms. A stereotactic frame is applied under local anesthetic parallel to the orbitomeatal line (which aligns with the anterior-posterior commissural **(AC-PC)** line).

Radiologic target localization

May utilize: MRI, CT, and/or ventriculography. MRI is the most common imaging modality, and may best demonstrate the desired anatomy, but is susceptible to geometric distortion. Therefore many centers also utilize CT and/or ventriculography to supplement MRI. T1WI images are commonly employed, however some feel that optimal MRI imaging may be performed with gadolinium-enhanced axial and coronal projections using 1 mm slice intervals and a STIR or spoiled GRASS volume acquisition protocol.

The posterior commissure is the white-matter band at the level of the pineal that crosses at the posterior third ventricle.

The typical initial target[27] is shown in *Table 19-1*. Avoid encroachment on internal capsule (medial to GPi) and optic tract (inferior to GPi). Lesions of the subthalamic nucleus are associated with hemiballismus. An entry site is chosen from imaging studies, and is usually just anterior to the coronal suture and 15-20 mm lateral to the midline. A 4 mm twist drill hole is used. The trajectory should

avoid midline venous structures, arterioles within sulci (therefore enter through a gyrus), and passage through the lateral ventricle.

Table 19-1 Target for pallidotomy

1. 1-3 mm anterior to the mid-point of the AC-PC line	**MEDIAN**
	2 mm
2. 18-23 mm lateral*	**21 mm**
3. 2-6 mm inferior	**5 mm**

* may be decreased in women (start at ≈ 19 mm), or increased when the 3rd ventricle is dilated

Electrophysiologic target localization

Stimulation:

The patient must be awake for the procedure. For patients with dyskinesias that occur only following a dose of medication, their normal dose of medicine is given after imaging to bring out the symptoms for the procedure. Stimulation is required to verify the neurophysiologic target which varies between individuals. Macroelectrode stimulation may be done with the lesioning electrode. Impedance typically drops when a white matter tract is encountered. The impedance of the desired target is usually > 600 Ω. Stimulate with square wave at 1, 5, 50 and 100 Hz with voltage range of 0.5-3 volts (NB: above ≈ 2 V you may be seeing wide-field stimulation). Pallidum stimulation usually increases (but occasionally decreases) contralateral muscle tone. Also look for reduction of tremor or dyskinesia. Contralateral weakness or hypotonia indicates proximity to the internal capsule. Visual scotomata suggests stimulation of the optic tract.

Micro-electrode recording:

About half the institutions surveyed perform microelectrode recording, and half the remaining centers were considering starting it.

Lesioning

Kondziolka et al.[22] use a 1.1 mm diameter probe with a 3 mm exposed tip. A small lesion is made at 45°C for 30 seconds, before making the definitive lesion at 70-80°C for 60 seconds. The probe is withdrawn 3-4 mm and a second lesion is made. Lesions with cryoprobes may be associated with a higher incidence of intracerebral hemorrhage.

For the very rare patient in whom insertion of an electrode is contraindicated

(e.g. refractory coagulopathy), lesioning may be done with stereotactic radiosurgery, however, this eliminates the critical ability to verify the site of the planned lesion electrophysio-logically before a permanent lesion is made.

Unilateral pallidotomy produces primarily contralateral effects, although some ipsilateral changes occur. Bilateral procedures are usually staged separately with a 3-12 hiatus between sides. Although they can been done in one sitting, bilateral pallidotomies may carry an increased risk of speech difficulties and cognitive decline.

Results

At present, the major focus of therapy has been on improvement of *motor* symptoms. Although 97% of patients showed at least some improvement (some poor results may derive from inclusion of some patients with secondary Parkinsonism), in 17% the degree of improvement was graded as mild.

Significant reduction of levodopa induced dyskinesias occurred in 90%. Bradykinesia improved in 85%, rigidity in 75%, and tremor in 57%. Other areas of improvement include: speech, gait, posture, and reduction of on-off phenomenon and freezing. Although symptoms may be ameliorated, overall functional improvement may not be remarkable[32].

Although dosages of antiparkinsonian medication are often reduced, continued medical therapy is usually required, and no change is made for at least 2 months following pallidotomy.

Indications are that beneficial surgical effects can last ≥ 5 years, with early failures possibly due to production of too small of a lesion, and late failures possibly due to progression of the disease.

Ongoing studies are investigating longer term results, microelectrode recording, alternate lesioning targets, the role of early surgery… Until more information is available, one cannot make any statements about the optimal target, localizing method, etc.

Complications

Visual field deficit occurs in 2.5% due to proximity of the optic tract to the globus pallidus. Hemiparesis may occur due to the nearby passage of the internal capsule. Intracerebral hemorrhage may also occur. Dysarthria occurs in ≈ 8%, but is usually temporary. Speech difficulties and also cognitive decline may be more risky when bilateral pallidotomies are performed at the same sitting.

THALAMIC LESIONS

Lesioning the thalamic ventralis intermedius nucleus **(VIM)** nucleus reduces Parkinsonian tremor in > 85%. It can also be useful in the treatment of rigidity and drug induced dyskinesias by extending the lesioning anteriorly to include the ventral oralis. However thalamotomy does not improve symptoms of akinesia or bradykinesia and can result in worsening of gait symptoms or speech problems.

SUBTHALAMOTOMY

Lesioning the subthalamic nucleus **(STN)** is classically associated with intractable hemiballism. There are few studies as a result, but the limited data suggests that selective lesioning in this region provides relief on par with pallidotomy. Postoperative hemichorea is a known complication but is generally transitory and mild[33]. DBS in this region may be a better option (*see page 532*).

19.3. Dystonia

Pallidal stimulation is the primary *surgical* treatment for dystonia[34]. Response is better for primary dystonias, e.g. tardive dystonias than for secondary dystonias such as postanoxic, postencephalitic, perinatal and poststroke dystonias[34] (other targets need to be assessed).

For primary dystonias, the globus pallidus internus **(GPi)** is the most common primary target (see *Figure 19-1*, page 533). Good results have also been reported with STN DBS.

19.4. Spasticity

Results from lesions in upper motor neuron pathway, causing absence of inhibitory influence on alpha motor-neurons **(αMN)** (alpha spasticity) as well as on gamma motor neurons (intrafusal fibers) (gamma spasticity). Causes uninhibited reflex arc between αMN and Ia afferents from muscle spindles resulting in a hypertonic state of muscles with clonus, and sometimes with involuntary movements. Etiologies include: injury to cerebrum (e.g. stroke) or spinal cord (spasticity is an expected sequelae of spinal cord injury rostral to the conus medullaris), multiple sclerosis, and congenital abnormalities (e.g. cerebral palsy, spinal dysraphism).

CLINICAL

Increased resistance to passive movement, hyperactive muscle stretch reflexes, simultaneous activation of antagonistic muscle groups, may occur spontaneously or in response to minimal stimuli. Characteristic postures include scissoring of legs or hyperflexion of thighs. May be painful, or may disrupt patient's ability to sit in wheel-chair, lay in bed, drive modified vehicles, sleep, etc. May also promote development of decubitus ulcers. A spastic bladder will have low capacity and will empty spontaneously.

Spasticity is often exacerbated by same type of stimuli that aggravate autonomic hyperreflexia (see *Autonomic hyperreflexia*, page 1000).

The onset of spasticity following spinal cord injury may be delayed for several days to months (the latency period is attributed to "**spinal shock**", during which time there is decreased tone and reflexes)[35] (*see page 930*). Onset of spasticity following spinal shock starts with increasing flexor synergistic activity over 3-6 mos, with more gradual increases of extensor synergy which ultimately predominates in most cases.

Some "beneficial" aspects of mild spasticity:

1. maintains muscle tone and therefore bulk: provides support for patient when sitting in wheelchair, helps prevent decubitus ulcers over bony prominences
2. muscle contractions may help prevent DVTs
3. may be useful in bracing

Grading spasticity

Assessment should be performed with patient supine and relaxed. The Ashworth scale (*see Table 19-2*) is commonly used for the clinical grading of the severity of spasticity. Many attempts have been made to quantitate spasticity electrodiagnostically, the most reliable has been H-reflex measurement.

Table 19-2 Ashworth scores[36]

Ashworth score	Degree of muscle tone
1	no increase in tone (normal)
2	slight increase, a "catch" with flexion or extension
3	more marked increase, passive movements easy
4	considerable increase, passive movements difficult
5	affected part rigid in flexion or extension

TREATMENT

Depends on extent of useful function (or potential for same) present in areas at and below the level where spasticity starts (complete spinal cord injuries usually have little function, whereas patients with MS may have significant function).

MEDICAL TREATMENT

1. "prevention": measures to decrease inciting stimuli (physical therapy to prevent joint damage, good skin & bladder care… see *Autonomic hyperreflexia*, page 1000)
2. prolonged stretching (more than just range of motion): not only prevents joint and muscle contractures, but modulates spasticity
3. oral medications[37] (see *Surgical treatment* below for intrathecal medications): few drugs are effective without significant undesirable side effects
   A. diazepam (Valium®): activates $GABA_A$ receptors, increases pre-synaptic inhibition of αMN. Most useful in patients with complete spinal cord injuries. ***Rx*** start with 2 mg PO BID-TID, increase by 2 mg per day q 3 days up to a max of 20 mg TID.

      SIDE EFFECTS: may cause sedation, weakness, decreased stamina (most of which may be minimized by gradual increases in dosage). Abrupt discontinuation may cause depression, seizures, withdrawal syndrome

   B. baclofen (Lioresal®): activates presynaptic $GABA_B$ receptors of Ia muscle spindle afferents, causes pre-synaptic inhibition of αMN and decreases nociception. May be most useful in patients with spinal cord lesions (complete or incomplete).

      Rx start with 5 mg PO BID-TID, increase in 5 mg increments q 3 days up to max of 20 mg QID. **SIDE EFFECTS:** sedation, lowers seizure threshold. Must be tapered to discontinue (abrupt discontinuation may result in seizures, rebound hyperspasticity or hallucinations).

   C. dantrolene (Dantrium®): reduces depolarization induced Ca^{++} influx into sarcoplasmic reticulum of skeletal muscle; acts on all skeletal muscle (with no preferential effect on spasmogenic reflex arc).

      Rx start with 25 mg PO q d, increase q 4-7 days to BID, TID, then QID, then by 25 mg per day up to max of ≈ 100 mg QID (may take 1 week at new steady state to see effect); **SIDE EFFECTS:** muscle

weakness (may make ambulation impossible), sedation, idiosyncratic hepatitis (may be fatal; more common in patients on > 300 mg/d x > 2 mos) that is often preceded by anorexia, abdominal pain, N/V; D/C if no benefit is seen by ≈ 45 days; follow LFTs (SGPT or SGOT)

D. progabide: activates both $GABA_A$ and $GABA_B$ receptors. Useful for patients with severe flexor spasms

E. theoretical benefits may be derived from other agents, but they have not been used for some practical reason in each case 35 (e.g. phenothiazines reduce gamma spasticity, but only at high PO doses or parenterally; clonidine; Darvon; tetrahydrocannabinal…)

Surgical treatment

Reserved for spasticity refractory to medical treatment, or where side effects of medications are intolerable. Generally either orthopedic (e.g. tendon release operations (tenotomies) of heel cord or hamstrings, iliopsoas myotomies, etc.) or neurosurgical (e.g. nerve blocks, neurectomies, myelotomy, etc.).

1. nonablative procedures
   - A. intrathecal **(IT)** baclofen (*see below*)
   - B. intrathecal morphine (tolerance and dependence may develop)
   - C. electrical stimulation via percutaneously placed epidural electrodes[38]
2. ablative procedures, with <u>preservation</u> of potential for ambulation
   - A. motor point block[35] (intramuscular phenol neurolysis): preserves sensation and existing voluntary function. Especially useful in patients with incomplete myelopathies; time consuming
   - B. phenol nerve block: similar to motor point block, but used when spasticity more severe and complete block of muscle desired. Open phenol block used instead of percutaneous when nerve is mixed and sensory preservation is desired (also reduces post-block dysesthesias)[39]
   - C. selective neurectomies[35]
     1. sciatic neurectomy (may be done with RF lesion)[40]
     2. obturator neurectomy: useful if strong hip adductor spasticity that causes scissoring and wasted energy expenditure in ambulating
     3. pudendal neurectomy: useful if excessive detrusor dyssynergy interferes with bladder retraining
   - D. percutaneous radiofrequency foraminal rhizotomy: small unmyelinated sensory fibers are more sensitive to RF lesions than

larger myelinated A-alpha fibers of motor units.

Technique: start at S1 on one side, and work up to T12, then repeat on other side. At each level: verify needle position by stimulating with 0.1-0.5 V and watch for movement in appropriate myotome (tip should be extradural, avoid subarachnoid placement), ablate with 70-80° C **x** 2 mins for S1, and 70° C x 2 mins for L5 to T12 (to preserve motor function). If symptoms recur, may repeat with lesions at 90° C x 2 mins

E. myelotomies[41]
   1. Bischof's myelotomy: divides anterior and posterior horns via laterally placed incision, disrupts reflex arc. No effect on α–spasticity
   2. midline "T" myelotomy: interrupts reflex arc from sensory to motor units without disrupting connections from corticospinal tract to anterior motor neurons. Slightly higher risk of losing motor function. *Technique*: laminectomy from T11 to L1. Mobilize midline dorsal longitudinal vein and incise cord in midline from T12 at a depth of 3 mm to S1 at a depth of 4 mm (preserving S2-S4 maintains bladder reflex pathways. Unilateral extension up to conus medullaris reduces bladder spasticity and increases capacity before reflex emptying occurs)

F. selective dorsal rhizotomy[42, 43]: uses intraoperative EMG and electrophysio-logical stimulation to eliminate sensory rootlets involved in "handicapping spasticity" (leaves rootlets subserving "useful spasticity" intact). Interrupts the afferent limb of pathologic reflex arc. May be temporary, but seems to persist at least ≈ 5 yrs. No effect on α–spasticity. Ambulatory children with cerebral palsy have improved gait, nonambulatory children are improved but are still not able to ambulate afterwards

G. stereotactic thalamotomy or dentatotomy: may be useful in cerebral palsy[44]. Useful for unilateral dystonia, but cannot be used for bilateral dystonia as bilateral lesions would be required which jeopardizes speech. Effective only for dystonia <u>distal</u> to shoulders or hips, and should not be used if the condition is rapidly progressive

3. ablative procedures, with <u>sacrifice</u> of potential for ambulation (in complete cord injuries, nonablative procedures are not indicated because there is no motor function to recover). Used after failure of percutaneous rhizotomy (*see above*) and "T" myelotomy (*see above*)

A. intrathecal injection of 6 ml of 10% phenol (by weight) in glycerin mixed with 4 ml of iohexol (Omnipaque® 300) (*see* *page 122*) for a final concentration of 6% phenol and ≈ 120 mg iodine/ml. Administered via LP at L2-3 interspace with patient in lateral decubitus position (most symptomatic side down) under fluoro until T12-S1 nerve root sleeves are filled (sparing S2-4 for bladder function). Patient is maintained in this position **x** 20-30 mins and then kept sitting upright **x** 4 hrs[45] (absolute alcohol provides more permanent blocks, but is hypobaric and more difficult to control)
B. selective anterior rhizotomy: results in flaccid paralysis with denervation atrophy of muscles
C. neurectomies, often combined with tenotomies[40]
D. intramuscular neurolysis by phenol injection[40]
E. cordectomy 46: most drastic measure, reserved for patients who do not respond to any other measure. Results in total flaccidity with loss of benefits from mild spasticity. Converts bladder from UMN to LMN control. Works well for progressive deficit from syringomyelia and for spasticity, but poor for "phantom" leg pain[47]
F. cordotomy: rarely used

Intrathecal baclofen[48-51]

Selection criteria used in one study[50] are shown in *Table 19-3*. Other indications include: CVA[52], cerebral palsy, TBI, dystonia, stiff-man syndrome.

Test doses: Incremental test doses of 50, 75, and then 100 mcg intrathecal baclofen **(ITB)** via lumbar puncture or temporary catheter were used[50], randomly alternated with placebo, with dose escalation halted if a response to active drug occurred. The following parameters were evaluated at 0.5, 1, 2, 4, 8 & 24 hrs post injection: pulse and respiratory rate, BP, hypertonia (Ashworth score, see *Table 19-2*, page 537), reflexes, spasm score, voluntary muscle movement, and adverse effects (if any, including seizures). Pump implantation was offered if there was a 2 point reduction in the Ashworth score and muscle spasm score for ≥ 4 hrs after bolus injection of active drug without intolerable side effects. Usual daily dose for ITB is twice the test dose, typically 200 micrograms/d.

Alternatively, give 25 mcg IT in the O.R., and if the patient improves, insert subcutaneous pump[37].

Table 19-3 Selection criteria for baclofen pump

• age 18-65 yrs (older patients treated on compassionate use basis)
• able to give informed consent
• severe, chronic spasticity (≥ 12 mos duration) due to spinal cord lesion or MS
• spasticity refractory to oral drugs (including baclofen), or unacceptable side effects
• no CSF block (e.g. on myelography)
• positive response to IT baclofen at test dose ≤ 100 µg and no response to placebo
• no implanted programmable device such as cardiac pacemaker*
• females of childbearing potential: not pregnant & using adequate contraception
• no hypersensitivity (allergy) to baclofen
• no history of stroke, impaired renal function, or severe hepatic or GI disease

* this study used a programmable IT pump

Pump systems: Available programmable systems include N'Vision, manufactured by Medtronic, Inc., Minneapolis, MN.

Insertion technique: IT catheter is typically inserted ≈ L2-3, and is threaded rostrally ≈ 3 levels, but should be no higher than T10 (risk of rostral progression of hypotonia).

Post-op orders: Guidelines for post-operative orders following baclofen pump insertion

1. admit PACU, transfer to:
   A. floor if insertion follows test dosing or if patient has just been transitioned from stable PO dose
   B. ICU if there has been a hiatus in baclofen therapy
2. neuro checks q 2 hrs for 1st 24 hours
3. baclofen:
   A. for patients on oral or IV baclofen: continue baclofen at the previous dose via the same route (oral or IV) until the ITB takes effect (usually 2-4 hrs, full effect is delayed up to 24 hrs). The IV/PO drug is then tapered
   B. if there has been a hiatus in baclofen therapy: baclofen 20 mg PO QID
4. have 2 vials of IV physostigmine available and labeled "FOR EMERGENCY USE ONLY" for possible baclofen overdose

Baclofen overdose:

1. ABCs (airway/breathing/circulation). Intubate if necessary
2. empty pump reservoir to stop drug flow (record amount withdrawn)

3. administer physostigmine if not contraindicated:
   A. ***Rx*** adult: 0.5-1.0 mg IM or IV @ rate ≤ 1 mg/min (may repeat q 10-30 minutes PRN)
   B. ***Rx*** peds: 0.02 mg/kg IM or IV @ rate ≤ 0.5 mg/min (may repeat q 5-10 min up to 2 mg max)
4. withdraw 30-40 ml CSF either via LP or through catheter access port
5. notify the pump manufacturer

Complications: Device-related complications are shown in *Table 19-4*. The frequency of most is ≈ 1%, except catheter-related problems which had a rate of ≈ 30% 50.

Complications related to the drug therapy itself include: overdosage problems (rostral progression of hypotonia, respiratory depression, coma, and seizures.

Table 19-4 ITB pump complications*

• mechanical problems
• pump underinfusion
• catheter problems: occlusion, kink, dislodgment, cut, break or disconnection
• wound complications
• pocket erosion
• incisional pain
• infection
• seroma (may require aspiration)
• CSF collection

* device-related complications requiring a secondary invasive procedure

Intrathecal baclofen withdrawal: Interruption of ITB therapy may occur as a result of: empty pump reservoir, pump battery failure, catheter migration/breakage/kinking/disconnection/occlusion, programming error. Steps in assessing the infusion system are shown in *Table 19-5*.

The severity of withdrawal syndrome depends on dose of drug used (increased with higher dose) and duration of therapy (increased with longer therapy).

Syndromes: with abrupt discontinuation of ITB

- mild withdrawal symptoms: return of spasticity and rigidity, tachycardia, piloerection (goosebumps) & pruritus
- more significant withdrawal symptoms: seizures & hallucinations
- severe withdrawal symptoms (estimated incidence: 3-5%)Coffey, 2002 #5531]:

increased rebound spasticity, rigidity, fever, labile BP, and reduced level of consciousness (resembling but distinct from malignant hyperthermia (*see* *page 5*) or neuroleptic malignant syndrome). If untreated, the severe syndrome can progress over 24-72 hours to rhabdomyolysis (with elevated creatine kinase (CK) and transaminase), hepatic and renal failure, DIC, and occasionally death

Table 19-5 Assessing ITB infusion systems

• interrogate the pump (with device programmer)
• refill reservoir with drug if empty (by experienced ITB practitioner)
• obtain AP & lateral x-rays to assess location of catheter tip and to look for breaks, kinks or migration

Management of abrupt ITB withdrawal syndrome[53]:

1. ABCs (airway/breathing/circulation). Intubate if necessary
2. primary goal is to reestablish ITB therapy at the same dose as soon as possible
3. assess pump/system as outlined in *Table 19-5*
4. early use of high-dose oral/enteral baclofen: ≥ 120 mg/d in 6-8 divided doses if the patient's condition permits (NB: PO baclofen is not reliable as the lone treatment for ITB withdrawal, and safety not established for age < 12 yrs)
5. attempt to restore ITB therapy at or near pre-withdrawal dosage by experienced physician by one of the following:
   A. using a programmed bolus through the pump
   B. via the catheter access port
   C. via LP
   D. via new externalized catheter
6. if restoration of ITB therapy is delayed and if symptoms persist
   A. move pt. to ICU if not already there
   B. parenteral benzodiazepine infusion: diazepam or midazolam. Titrate dose to reduce muscle rigidity, hyperthermia, BP lability, seizures
   C. cyproheptadine[54]: a serotonin antagonist. Start with 4 mg po q 6 hrs
   D. diphenhydramine 50 mg PO or IM, may repeat q 6 hrs for pruritus
   E. dantrolene may not be as effective as it is for malignant hyperthermia

If it is necessary to electively (or semi-electively) remove a pump system, the optimal scenario is to gradually taper the drug by reprogramming the pump and/or by filling the reservoir with solution of decreased baclofen concentration.

19.5. Torticollis

AKA wry neck. A form of dystonia resulting in a failure to control head position (if shoulders or trunk are also involved, *dystonia* is a more proper label).

A symptom of diverse causes. Differential diagnosis includes:

1. congenital torticollis (may be the initial presentation of dystonia musculorum deformans)
2. **spasmodic torticollis**, AKA wry neck: a specific subtype of torticollis that is idiopathic by definition. The shortened sternocleidomastoid **(SCM)** muscle is usually in spasm
3. extrapyramidal lesions (including degenerative): often alleviated by lying down; EMG shows abnormal grouped activity
4. psychogenic (often mentioned, seldom verified)
5. torticollis from atlantoaxial rotatory subluxation: (*see page 955*) the <u>elongated</u> SCM may be in spasm (opposite of that in spasmodic torticollis)
6. neurovascular compression of the 11th nerve (*see below*)
7. hemorrhage into sternocleidomastoid muscle (with subsequent contracture)
8. infection of the cervical spine
9. cervical adenitis
10. syringomyelia
11. cerebellar tumors in children
12. bulbar palsies
13. “pseudotorticollis” may develop as an unconscious correction to reduce diplopia that occurs with imbalance of extraocular eye musculature

Non-surgical treatment of torticollis

Should be attempted first, and includes:

1. relaxation training, including biofeedback
2. thorough neuropsychiatric evaluation
3. trans-epidermal neuro-stimulation **(TENS)** to the neck

Surgical procedures

Reserved for disabling, refractory cases. Includes:

1. dorsal cord stimulation
2. local injection of botulinum toxin: may work for retrocollis, is poor for lateral torticollis (must inject posterior cervicals and both SCM, and may cause temporary pharyngeal muscle dysfunction resulting in dysphagia), and is totally ineffective for anterocollis
3. selective rhizotomy and spinal accessory nerve section

Other treatments for torticollis include

1. stereotactic electrocoagulation of Forel's H_1 field

TORTICOLLIS OF 11TH NERVE ORIGIN

1. usually a horizontal type (manifests as horizontal head movement) which may be exacerbated when supine (unlike extrapyramidal torticollis)
2. contraction of SCM is usually accompanied by activity in contralateral agonist muscles
3. may be treated surgically. Procedures include
   A. sectioning of the anastomotic branches between the 11th nerve and the upper cervical posterior root (C_1 anastomotic branch is sensory only)
   B. microvascular decompression of the 11th nerve (most cases caused by vertebral artery, but PICA compression is also described[55]). Relief takes several weeks post-op

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19.6. Neurovascular compression syndromes

Syndromes due to compression of cranial nerves at the root entry zone **(REZ)** (or in the case of motor nerves, root *exit* zone). The REZ (AKA Obersteiner-Redlich zone) is the point where central myelin (from oligodendroglial cells) changes to peripheral myelin (from Schwann cells).

Syndromes include:

1. trigeminal neuralgia (see *Trigeminal neuralgia*, page 551)
2. hemifacial spasm: *see below*
3. disabling positional vertigo
4. some forms of torticollis of 11th nerve origin (see *Torticollis* above)

19.6.1. Hemifacial spasm

Key concepts:

- intermittent unilateral painless contractions of facial muscles
- typically caused by compression of VII nerve by AICA
- along with palatal myoclonus: the only movement disorder that persists in sleep
- responds well to microvascular decompression, but risk of hearing loss is ≈ 20%

Hemifacial spasm **(HFS)** is a condition of intermittent, painless, involuntary, spasmodic contractions of muscles innervated by the facial nerve in one side of the face only. May be limited to the upper or lower half of the face only, and excess lacrimation may be present. HFS usually begins with rare contractions of the orbicularis oculi, and slowly progresses to involve the entire half of the face and increases in frequency until the ability to see out of the affected eye is impaired.

HFS may be associated with trigeminal neuralgia, geniculate neuralgia (see *Tic convulsif* page 564), or vestibular and/or cochlear[56] nerve dysfunction.

HFS is more common in women, is seen more often on the left, and usually presents after the teenages. Auditory function testing reveals abnormal acoustic middle ear reflex in almost half of patients, indicating some degree of VIII compromise[56].

Meige's syndrome: hemifacial spasm with oral movements.

HFS and **palatal myoclonus** are the only involuntary movement disorders that persist during sleep[57].

ETIOLOGIES

1. vascular compression syndrome (*see below*): the most common etiology (much more common than with trigeminal neuralgia)
2. idiopathic
3. tumor compressing the nerve
4. can follow some cases of Bell's palsy
5. conditions that can mimic HFS
    A. **blepharospasm** (bilateral spasmodic closure of the orbicularis oculi

muscles) which is more common in the elderly, and may be associated with organic brain syndrome. Blepharospasm is notorious for disappearing when the patient presents for medical evaluation (an effect of alerting), but may be elicited by asking patient to gently close the eyes and then rapidly open them, following which a blepharospasm may occur. HFS usually involves more than the ocular muscles

B. **facial myokymia**: *continuous* facial spasm which may be a manifestation of an intrinsic brainstem glioma or of multiple sclerosis. Often associated with other findings

Vascular compression

HFS is usually caused by compression of the facial nerve at the root exit zone **(REZ)** by a vessel, which is most often an artery (most commonly AICA[58] (either pre- or postmeatal[59]), but other vascular possibilities include an elongated PICA, SCA, a tortuous VA, the cochlear artery, a dolichoectatic basilar artery, AICA branches…), aneurysm, a vascular malformation, and rarely, veins have been implicated. In typical HFS (onset in the orbicularis oculi, and progressing downward over the face), the vessel impinges on the antero-caudal aspect of the VII/VIII nerve complex, in atypical HFS (beginning in the buccal muscles and progressing upward over the face) the compression is rostral or posterior to VII[60].

Vessels contacting the REZ of the vestibular nerve may cause vertigo, whereas tinnitus or hearing loss may result from cochlear nerve REZ compression.

Infrequently, benign tumors or a cyst in the cerebellopontine angle, multiple sclerosis, adhesions, or osseous skull deformities will be the cause of HFS.

Evidence indicates that there is not cross (ephaptic) conduction at the compressed REZ, but that the facial motonucleus is involved secondarily as a result of the REZ compression, via a phenomenon similar to kindling[61]. In addition to the spasm, a 2nd electro-physiological phenomenon associated with HFS is **synkinesis**, where stimulation of one branch of the facial nerve results in delayed discharges through another branch (average latency: 11 mSec[62]).

EVALUATION

In typical cases of HFS, the diagnostic work-up is negative.

Most patients should have MRI of the posterior fossa (CT scan is less sensitive here) to R/O tumors or AVMs.

Vertebral angiography is usually not performed if imaging is normal. The neurovascular compression responsible for HFS usually cannot be identified on angiography.

TREATMENT

MEDICAL MANAGEMENT

HFS is generally a surgical condition. Early, mild cases may be managed expectantly. Carbamazepine and phenytoin are generally ineffective, unlike the situation with the causally similar condition of trigeminal neuralgia. Local injection of **botulinum toxin** (Oculinum®) may be effective in treating HFS and/or blepharospasm[63, 64]. Baclofen has been advocated but is not very effective.

SURGICAL MANAGEMENT

Many ablative procedures are effective for HFS (including sectioning of divisions of the facial nerve), however, this leaves the patient with some degree of facial paresis. The current procedure of choice for HFS is microvascular decompression **(MVD)** wherein the offending vessel is physically moved off of the nerve, and a sponge (e.g. Ivalon®, polyvinyl formyl alcohol foam) is interposed as a cushion. Other cushions may not prove to be as satisfactory (muscle may disappear, and Teflon felt may thin[65]).

Most often, the offending vessel approaches the nerve at a right angle, and causes grooving in the nerve. Compression must occur at the root exit zone; decompression of vessels impinging distal to this area is usually ineffective.

Operative risks: *see below*.

Post-operatively, there may be episodes of mild HFS, however they usually begin to diminish 2-3 days following MVD. Severe spasm that does not abate suggests failure to achieve adequate decompression, and reoperation should be considered.

Surgical results of MVD depends on the duration of symptoms (shorter duration has better prognosis) as well as on the age of the patient (elderly patients do less well). Complete resolution of HFS occurred in 44 (81%) of 54 patients undergoing MVD, however, 6 of these patients had relapse[66]. 5 patients (9%) had partial improvement, and 5 (9%) had no relief.

Technique of MVD

Intraoperative brainstem auditory evoked potential (BAER)[67], or more applicable, direct VIII nerve monitoring[68] may help prevent hearing loss during MVD for 7th or 8th nerve dysfunction. Furthermore, monitoring for the disappearance of the (delayed) syn-kinetic response may aid in determining when adequate decompression has been achieved (generally reserved for teaching institutions)[61].

For a diagram of the normal anatomy of the CPA, see *Figure 5-8*, page 90. The facial nerve should not be manipulated, and one should avoid dissection around the VII and VIII nerves near the IAC[69]. Vessels must be preserved, especially the cochlear artery and small perforators.

Place gentle medial traction on the cerebellum (< 1 cm is recommended[69]), and incise the arachnoid membrane between the flocculus and the eighth nerve (to avoid tension on nerves that could cause post-op deficit). The IX nerve may be followed medially from the jugular foramen to locate the origin of the VII nerve (the origin of VII is 4 mm cephalad and 2 mm anterior to that of the IX nerve[70]).

SURGICAL RESULTS

Complete resolution of spasm occurs in ≈ 85-93%[65, 71-74]. Spasm is diminished in 9%, and unchanged in 6%[74]. Of 29 patients with complete relief, 25 (86%) had immediate post-op resolution, and the remaining 4 patients took from 3 mos to 3 yrs to attain quiescence.

Recurrence

Return of symptoms after a period of complete resolution of HFS occurs in up to 10% of patients, 86% of recurrences happen within 2 yrs of surgery, and the risk of developing recurrence after 2 yrs of post-op relief is only ≈ 1%[74].

Surgical complications

1. ipsilateral hearing loss: may occur from traction injury or a vasospasm
   A. total hearing loss occurs in ≈ 13% (range: 1.6-15%) (2.8% in one series[56], 15% in another series[66])
   B. partial hearing loss: 6%
2. facial weakness
   A. transient: 18%
   B. permanent facial weakness: 6%[72]

3. ataxia in 1-6%
4. other complications that are minor or temporary include:
   A. aseptic meningitis (AKA hemogenic meningitis) in 8.2%
   B. hoarseness or dysphagia in 14%
   C. CSF rhinorrhea in 0.3%
   D. perioral herpes in 3%[69]

19.7. Hyperhidrosis

Either essential (primary, or idiopathic) or secondary (etiologies include: hyperthyroidism, diabetes mellitus, pheochromocytoma, acromegaly, parkinsonism, CNS trauma, syringomyelia, hypothalamic tumors, menopause)[75].

Due to overactivity of eccrine sweat glands (found over entire body, highest concentration in palms and soles of feet). They produce a hypotonic secretion with saline as the primary constituent. These glands are under control of the sympathetic nervous system, however, the neurotransmitter is paradoxically acetylcholine (i.e. they are cholinergic, unlike most sympathetic end organs which are adrenergic). Most eccrine sweat glands serve a thermoregulatory function, however, those on the palms and soles respond primarily to emotional stress[75].

Essential hyperhidrosis is a generalized condition that usually manifests mostly in the palms. The incidence is unknown, although it was ≈ 1% in an Israeli study (probably high).

Treatment

Mild cases are treated medically with:

1. topical agents: astringents (potassium permanganate, tannic acid…) or antiperspirants (contact dermatitis usually limits use of these agents)
2. or systemically with anticholinergics: including atropine, probantheline bromide… (side effects of dry mouth and blurred vision usually limits use of these)
3. tap water iontophoresis: may produce keratinization of palmar epithelium

Severe cases refractory to medical therapy may be candidates for surgical sympathectomy (*see below*).

19.8. Tremor

Thalamotomy or thalamic stimulation may be useful for tremors that are refractory to medical treatment (including parkinsonian (*see page 534*), essential[76, 77], cerebellar and post-traumatic)[30].

19.9. Sympathectomy

Cardiac sympathectomy

With the advances in percutaneous coronary artery techniques, cardiovascular surgery and drugs, cardiac sympathectomy for angina pectoris has found less application. However, it may still be useful in patients who have no further treatment options. Bilateral sympathectomy from the stellate ganglion through the T7 ganglia is required. Newer thoracoscopic techniques may revive some interest in this.

UPPER EXTREMITY SYMPATHECTOMY

Various pathologies that may be indications for upper extremity sympathectomy are shown in *Table 19-6*.

Removal of the only second thoracic ganglion is probably adequate, and avoids a Horner's syndrome in most. Techniques used include: anterior transthoracic, thoracic endoscopic[78], percutaneous radiofrequency, and supraclavicular. An approach via a midline posterior incision with a T3 costotransversectomy allows bilateral access[75, 79]. The risk of significant complications is ≈ 5% and include pneumothorax, intercostal neuralgia, spinal cord injury, and Horner's syndrome.

Table 19-6 Indications for UE sympathectomy

- essential hyperhidrosis
- primary Raynaud's disease
- shoulder-hand syndrome
- intractable angina
- ± causalgia major (*see page 576*)

UPPER THORACIC SYMPATHECTOMY

Approaches include:

1. posterior paravertebral approach
2. axillary thoracotomy with transthoracic exposure of the sympathetic chain
3. supraclavicular, retropleural exposure
4. percutaneous radiofrequency technique[80, 81]
5. video endoscopic approach[82]

LUMBAR SYMPATHECTOMY

Primary indication is for causalgia major of the lower extremity. Preoperative lumbar sympathetic blocks may be utilized to evaluate patient for response.

Removal of the L2 and L3 sympathetic ganglion is usually adequate to remove sym-pathetic tone from the lower extremities (occasionally L1 and sometimes T12 are also removed for causalgia of the thigh).

The most common approach is a retroperitoneal approach through a flank incision. The patient is placed in a lateral oblique position, and the skin incision is made from the anterior superior iliac spine to the tip of the 12th rib. The peritoneum is dissected from the muscular wall and is retracted anteriorly. The kidney and ureter are retracted anteriorly; injury to the ureter being a major risk of the operation. The sympathetic chain is identified on the lateral aspect of the vertebral bodies. The vena cava makes a right-sided approach more difficult as the aorta is easier to deal with on left-sided approaches.

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20. Pain

For pain medication, see *Analgesics*, page 44.

Major types of pain:

1. nociceptive
   A. somatic: well localized. Described as sharp, stabbing, aching or cramping. Results from tissue injury or inflammation, or from nerve or plexus compression. Responds to treating the underlying pathology or by interrupting the nociceptive pathway
   B. visceral: poorly localized. Poor response to primary pain medications
2. deafferentation: poorly localized. Described as crushing, tearing, tingling or numbness. Also causes burning dysesthesia numbness often with lancinating pain, and hyperpathia. Unaffected by ablative procedures
3. "sympathetically maintained" pain and the likes (e.g. causalgia): *see page 576*

20.1. Neuropathic pain syndromes

Definition: Neuropathic pain: pain caused by a lesion of the peripheral and/or central nervous system manifesting with sensory symptoms and signs[A].

A. Backonja[1] modified from the International Association for the Study of Pain[2]

Neuropathic pain syndromes **(NPS)** are typified by painful diabetic neuropathy **(PDN)** and postherpetic neuralgia **(PHN)**. Common chronic NPSs are shown in *Table 20-1*[3], divided into central or peripheral nervous system origin of the pain. The pain of PDN and PHN is typically burning and aching, and is continuous. and is characteristically refractory to medical and surgical treatment.

Table 20-1 Common neuropathic pain syndromes

Peripheral neuropathic pain
acute & chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
alcoholic polyneuropathy
chemotherapy induced polyneuropathy
complex regional pain syndrome (CRPS)
entrapment neuropathies
HIV sensory neuropathy
iatrogenic neuralgias (e.g. postthoracotomy pain)
idiopathic sensory neuropathy
neoplastic nerve compression or infiltration
nutritional-deficiency neuropathies
painful diabetic neuropathy (PDN)
phantom limb pain
postherpetic neuralgia (PHN)
postradiation plexopathy
radiculopathy toxic exposure-related neuropathies
trigeminal neuralgia
posttraumatic neuralgias
Central neuropathic pain
cervical spondylotic myelopathy
HIV myelopathy
multiple sclerosis-related pain
Parkinson disease-related pain
postischemic myelopathy
postradiation myelopathy
poststroke pain
posttraumatic spinal cord injury pain
syringomyelia

MEDICAL TREATMENT OF NEUROPATHIC PAIN

Treatment traditionally includes narcotic analgesics[4], and tricyclic antidepressants (*see below*). For further details and other treatment measures, *see page 796* for PDN, and *page 565* for PHN.

Tricyclic antidepressants: Use is often limited by anticholinergic and central effects and by limited pain relief[5, 6]. Possibly because serotonin potentiates the analgesic effect of endorphins and elevates pain thresholds, serotonin re-uptake blockers are more effective than norepinephrine re-uptake blockers, e.g. tranzodone (Desyrel®) blocks only serotonin. Also useful: amitriptyline (Elavil®) 75 mg daily; desipramine (Norpramin®) 10-25 mg/d; doxepin (Sinequan®) 75-150 mg/d. Some benefit may also derive from the fact that many patients with chronic pain are depressed. **SIDE EFFECTS:** anticholinergic effects and orthostatic hypotension, especially in the elderly. ✖ Not recommended for use in patients with ischemic heart disease.

Gabapentin: Effective in postherpetic neuralgia **(PHN)** (*see page 566*) and

painful diabetic neuropathy. Benefit also reported in pain associated with: trigeminal neuralgia, cancer[7], multiples sclerosis, HIV-related sensory neuropathy, CRPS, spinal cord injury, post-operative state[8], migraine[9] (a number of these studies may have been sponsored by the manufacturer[10]). See *page 416* for side effects, dosing & availability…

Lidocaine patch (Lidoderm®): may be effective[3]. ***Rx***: apply patch for up to 12 hrs/day up to a maximum of 3 patches at a time to the intact skin over the most painful area (may trim patch to appropriate size). **SUPPLIED**: 5% lidocaine (*see page 566*).

Tramadol (Ultram®): A centrally acting analgesic[3] (*see page 47*).

20.2. Craniofacial pain syndromes

Possible pathways for facial pain include: trigeminal nerve (portio major as well as portio minor (motor root)), facial nerve (usually deep facial pain), and eighth nerve[11]. Etiologies (adapted[12 (p 2328), 13]).

1. cephalic neuralgias
    A. trigeminal neuralgia (*see below*)
        1. vascular compression of V at root entry zone: the most common cause
        2. MS: plaque within V nerve
    B. glossopharyngeal neuralgia: pain usually in base of tongue and adjacent pharynx (*see page 563*)
    C. geniculate neuralgia: otalgia and deep prosopalgia (*see page 563*)
    D. **tic convulsif**: geniculate neuralgia with hemifacial spasm (*see page 564*)
    E. occipital neuralgia: *see page 804*
    F. superior laryngeal neuralgia: a branch of the vagus, results primarily in laryngeal pain and occasionally pain on the auricle
    G. sphenopalatine neuralgia
    H. herpes zoster: pain is continuous (not paroxysmal). Characteristic vesicles and crusting usually follow pain, most often in distribution of V_1 (isolated V_1 TGN is rare). In rare cases without vesicles, diagnosis may be difficult

I. postherpetic neuralgia (Ramsay-Hunt syndrome): *see page 564*
J. supraorbital neuralgia (SON) (*see page 562*)
K. trigeminal neuropathic pain (AKA trigeminal deafferentation pain)[13]: may follow injuries from sinus or dental surgery, head trauma
L. trigeminal deafferentation pain: follows trigeminal denervation including therapeutic measures to treat trigeminal neuralgia[13]
M. short-lasting unilateral neuralgiform headache with conjunctival injection and tearing **(SUNCT)**[14]: rare. Usually affects males 23-77 years old. Brief (< 2 minutes) pain (burning, stabbing or shock-like) usually near the eye, occurring multiple times per day. Associated autonomic findings (the "hallmark of SUNCT"): ptosis, conjunctival injection, lacrimation[A], rhinorrhea, hyperemia. May be due to CPA AVM. Microvascular decompression or trigeminal rhizotomy may be effective in some cases refractory to medical treatment with AEDs or corticosteroids

2. ophthalmic pain
   A. Tolosa-Hunt syndrome (*page 837*): painful ophthalmoplegia
   B. (Raeder's) paratrigeminal neuralgia (*page 838*): unilateral Horner's syndrome + trigeminal neuralgia
   C. orbital pseudotumor (*page 837*): proptosis, pain, and EOM dysfunction
   D. diabetic (oculomotor) neuritis
   E. optic neuritis
   F. iritis
   G. glaucoma
   H. anterior uveitis
3. otalgia (*see below*)
4. masticatory disorders
   A. dental or periodontal disease
   B. nerve injury (inferior and/or superior alveolar nerves)
   C. temporo-mandibular joint **(TMJ)** dysfunction
   D. elongated styloid process
   E. temporal & masseter myositis
5. vascular pain syndromes
   A. migraine headaches: see *Migraine*, page 57
      1. simple migraine

a. classic
b. common
2. complicated migraine
a. hemiplegic
b. ophthalmoplegic
B. cluster H/A (subtypes: episodic, chronic, chronic paroxysmal hemicrania) (*see page 58*)
C. giant cell arteritis (temporal arteritis): *see page 74*. Tenderness over STA
D. toxic or metabolic vascular H/A (fever, hypercapnia, EtOH, nitrites, hypoxia, hypoglycemia, caffeine withdrawal)
E. hypertensive H/A
F. aneurysm or AVM (due either to mass effect or hemorrhage)
G. carotidynia: e.g. with carotid dissection (*see page 1162*)
H. basilar dolichoectasia with fifth n. compression or indentation of the pons
6. sinusitis (maximally, frontal, ethmoidal, sphenoidal)
7. dental disease
8. neoplasm: may cause referred pain or fifth nerve compression
A. extracranial
B. intracranial tumor: primarily posterior fossa lesions, neoplastic compression of trigeminal nerve usually causes sensory deficit (see *Tumors and trigeminal neuralgia*, page 552)
9. atypical facial pain **(AFP)** (prosopalgia): traditionally a "wastebasket" category used for many things. It has been proposed[13] to reserve this term for a psychogenic disorder. May be suspected by
10. primary (nonvascular) H/A: including
A. tension (muscle contraction) H/A
B. post-traumatic H/A

A. lacrimation (the most common) or other autonomic signs may occur in V1 trigeminal neuralgia but are usually mild, and appear only in the later stages of the condition and with long lasting attacks[15]. Dramatic lacrimation and conjunctival injection from the onset of symptoms with SUNCT are the best characteristics to distinguish this from trigeminal neuralgia[16]. May also occur in cluster headache (*see page 58*)

Otalgia

Because of redundant innervation of the region of the ear, primary otalgia may have its source in the 5th, 7th, 9th, or 10th cranial nerves or the occipital nerves[17]. As a result, sectioning of the 5th, 9th or 10th nerve or a component of the 7th (nervus intermedius, chorda tympani, geniculate ganglion) has been performed with varying results[18]. Also, microvascular decompression **(MVD)** of the corresponding nerve may also be done[19].

Work-up includes: neurotologic evaluation to rule out causes of secondary otalgia (otitis media or externa, temporal bone neoplasms…). CT or MRI should be done in any case where no cause is found.

Primary otalgia

Primary otalgia is unilateral in most (≈ 80%). Trigger mechanisms are identified in slightly more than half, with cold air or water being the most common[18]. About 75% have associated aural symptoms: hearing loss, tinnitus, vertigo. Pain relief upon cocainization or nerve block of the pharyngeal tonsils suggests glossopharyngeal neuralgia (*see page 563*), however, the overlap of innervation limits the certainty.

An initial trial with medications used in trigeminal neuralgia (carbamazepine, phenytoin, baclofen…, *see page 552*) is the first line of defense. In intractable cases not responding to pharyngeal anesthesia, suboccipital exploration of the 7th (nervus intermedius) and lower cranial nerves may be indicated. If significant vascular compression is found, one may consider MVD alone. If MVD fails, or if no significant vessels are found, Rupa et al. recommend sectioning the nervus intermedius, the 9th and upper 2 fibers of 10th nerve, and a geniculate ganglionectomy (or, if glossopharyngeal neuralgia is strongly suspected, just 9th and upper 2 fibers of 10th)[18].

20.2.1. Trigeminal neuralgia

Key concepts:

- sharp. electric shock-like paroxysmal lancinating pain in the distribution of one or more branches of the trigeminal nerve on <u>one side</u>
- characterized by periods of remission and initial response to carbamazepine
- neurologic exam must be intact (only exception: mild sensory loss)
- 80-90% of cases are caused by compression of the trigeminal nerve at the

root entry zone by the superior cerebellar artery (SCA). In MS patients, may be due to MS plaque (MS patients are usually less responsive to procedures)
- 75% will ultimately fail medical therapy and require a procedure (main options: microvascular decompression, percutaneous rhizotomy or radiosurgery). Choice of modality depends on patient age, location of symptoms, prior treatment…

Trigeminal neuralgia **(TGN)** (AKA **tic douloureux**): paroxysmal lancinating electric-like pain lasting a few seconds, often triggered by sensory stimuli, confined to the distribution of one or more branches of the trigeminal nerve (*see Figure 20-1*) on one side of the face, with no neurologic deficit. The term "**atypical facial pain**" **(AFP)** is sometimes used to describe any other type of facial pain.

Rarely, TGN manifests as **status trigeminus**, a rapid succession of tic-like spasms triggered by seemingly any stimulus. IV carbamazepine (where available) or phenytoin may be effective for this.

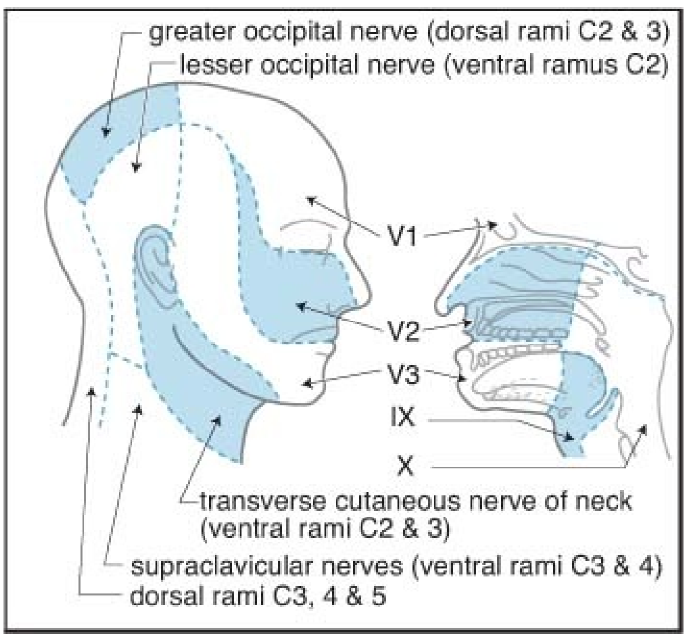

Figure 20-1 Pain/temperature innervation of the head*

* **KEY: V1** = ophthalmic nerve; V2 = maxillary nerve; V3 = mandibular nerve; IX = glossopharyngeal nerve; X = vagus

Epidemiology

See *Table 20-2*. Annual incidence 4/100,000. There is no correlation with herpes simplex infection[20]. There is a tendency for spontaneous remission with

pain free intervals of weeks or months being characteristic, regardless of treatment. 2% of patients with MS have TGN[21], whereas ≈ 18% of patients with bilateral trigeminal neuralgia have MS[22].

Pathophysiology

Probably due to ephaptic transmission in trigeminal nerve from large-diameter partially demyelinated A fibers to thinly myelinated A-delta and C (nociceptive) fibers. Pathogenesis may be due to:

1. vascular compression of the trigeminal nerve at the root entry zone (NB: compression may be seen in up to 50% of autopsies in patients without TGN[25]):
   A. most commonly (80%) by the SCA (see *Neurovascular compression syndromes*, page 542 for more details)
   B. persistent primitive trigeminal artery[26] (*see page 107*)
   C. dolichoectatic basilar artery[27 (p 1108)]
2. posterior fossa tumor (see *Tumors and trigeminal neuralgia* below)
3. in MS, plaque within brainstem may cause TGN that is often poorly responsive to microvascular decompression

In addition to the sensory division of the trigeminal nerve, other possible pain path-ways include[11]: the motor branch of the 5th nerve (portio minor), or the 7th or 8th nerve.

Evaluation

MRI is often used to evaluate these patients for possible intracranial tumors or MS plaques, especially in cases with atypical features. The yield in typical cases is low.

Table 20-2 Epidemiology of trigeminal neuralgia[23, 24]

age (years)	typically > 50 (average 63)
female:male	1.8:1
Laterality	
right	60%
left	39%
both	1%
Division involved	
V1 only	2%

V2 only	20%
V3 only	17%
V1 & V2	14%
V2 & V3	42%
all three	5%

Differential diagnosis

See *Craniofacial pain syndromes* on page 549.

History and physical (in addition to routine)

- history
  A. accurate description of pain localization to determine which divisions of trigeminal nerve need to be treated
  B. determine time of onset of TGN, trigger mechanisms
  C. ascertain presence and length of pain-free intervals (lack of any pain-free interval is atypical for TGN)
  D. determine duration, side-effects, dosages, and responses to medications tried
  E. inquire about symptoms that may indicate the presence of conditions other than TGN: e.g. history of herpetic vesicles, excessive tearing of the eye (may indicate SUNCT (*page 549*)), facial twitching (tic convulsif), tongue pain (glossopharyngeal neuralgia), sensory loss (tumor…), progressive relentless pain (tumor, herpes…), symptoms that suggest MS
- physical exam: the exam should be normal in TGN, any neurologic deficit (except very mild sensory loss) in previously unoperated patient should prompt search for structural cause, e.g. tumor (*see below*). This exam also serves as a baseline for post-op comparison
  A. assess sensation in all 3 divisions of trigeminal nerve bilaterally (include corneal reflexes)
  B. assess masseter function (bite) and pterygoid function (on opening mouth, chin deviates to weak side)
  C. assess EOM function

Tumors and trigeminal neuralgia

In > 2000 patients with facial pain seen over 10 yrs, only 16 harbored tumor

(< 0.8% incidence)[28]. 3 tumors outside cranial vault included nasal carcinoma and skull base mets; all had hypalgesia and AFP. 6 middle fossa tumors included 2 meningiomas, 2 schwannomas (1 primary tumor of Gasserian ganglion), and 1 pituitary adenoma. Posterior fossa tumors are the most likely to cause symptoms that most closely resemble true TGN; of these, vestibular schwannoma **(VS)** is most common. 2 of 7 VSs had tumors contralateral to the neuralgia (presumably due to brainstem shift). Patients with true TGN initially responded to carbamazepine, none with AFP did.

When facial pain is caused by tumor, especially with peripheral tumors, the pain is frequently atypical (usually constant), neurologic abnormalities are often present (usually sensory loss, although some are neurologically normal at first), and the age is often younger than typical TGN.

MEDICAL THERAPY FOR TRIGEMINAL NEURALGIA

carbamazepine (Tegretol®) DRUG INFO

Complete or acceptable relief in 69% (if 600-800 mg/d are tolerated and give no relief, diagnosis of TGN is suspect[21]). **SIDE EFFECTS:** Drowsiness. Rash in 5-10%. Possible Stevens-Johnson syndrome. Relative leukopenia is common (usually does not require discontinuing drug). See precautions under *carbamazepine (CBZ) (Tegretol®)* on page 411.

Rx 100 mg PO BID, increase by 200 mg/d up to maximum of 1200 mg/d divided TID. **SUPPLIED**: *see page 411*.

oxcarbazepine (Trileptal®) DRUG INFO

Rapidly metabolized to carbamazepine, similar efficacy, often tolerated at higher doses than carbamazepine. **SIDE EFFECTS:** symptomatic hyponatremia.

Rx for trigeminal neuralgia: 300 mg PO BID, increase by 600 mg/d q week. Usual dose: 450-1200 mg. Maximum of 2400 mg/d. **SUPPLIED**: 150, 300, 600 mg tablets; 500 mg/5-ml suspension.

baclofen (Lioresal®) DRUG INFO

2nd DOC (not as effective as carbamazepine, but fewer side-effects).

Caution: teratogenic in rats. Avoid abrupt withdrawal (can cause hallucinations and seizures). May be more effective if used in conjunction with low dose carbamazepine.

Rx Start low, 5 mg PO TID, increase q 3 d by 5 mg/dose; not to exceed 20 mg QID (80 mg/d); use smallest effective dose.

gabapentin (Neurontin®) **DRUG INFO**

An anticonvulsant (*see page 416*), may act synergistically with carbamazepine and baclofen. **SIDE EFFECTS:** include ataxia, sedation and rash.

Rx start with 100mg po BID, titrate to 5-7mg/kg/day (3600 mg/d max).

MISCELLANEOUS DRUGS

Also possibly effective:

1. phenytoin (Dilantin®): may be useful IV in patients in too much pain to open their mouths to take carbamazepine orally (*see page 409* for dosages)
2. capsaicin (Zostrix®): 1 gm applied TID for several days resulted in remission of symptoms in 10 of 12 patients (4 relapsed in < 4 mos, but remained pain free for 1 yr after 2nd course)[29]
3. clonazepam (Klonopin®): works in 25% (*see page 415*)
4. lamotrigine (Lamictal®)
5. amitriptyline (Elavil®): more commonly used for atypical facial pain
6. **botulinum toxin** (Botox®): reduces transmission of CGRP producing a direct effect on the sensory nerve fibers

SURGICAL THERAPY FOR TRIGEMINAL NEURALGIA

Reserved for cases refractory to medical management, or when side effects of medications exceed risks and drawbacks of surgery.

SURGICAL OPTIONS

1. peripheral trigeminal nerve branch procedures to block or ablate the division involved with pain, or can be used to block the trigger[30]:
   A. means of blocking
      1. local blocks (phenol, alcohol) s
      2. neurectomy of trigeminal branch involved

B. nerve branches:
   1. V1 (ophthalmic division) at the supraorbital, supratrochlear, or infraorbital nerves
   2. V2 (maxillary division) at the foramen rotundum
   3. V3 (mandibular division) block at the foramen ovale, or neurectomy of inferior dental nerve
2. blocking the trigger: either via percutaneous rhizotomy or alcohol block
3. **percutaneous trigeminal rhizotomy (PTR)**: AKA percutaneous (stereotactic) rhizotomy **(PSR)** of trigeminal (Gasserian) ganglion (*see below*) (not truly a stereotactic procedure in the current sense of the word, therefore the term *percutaneous trigeminal rhizotomy* is preferred). Objective is to selectively destroy A-delta and C fibers (nociceptive) while preserving A-alpha and beta fibers (touch). Ideally, a retrogasserian lesion (not a ganglionic lesion). May also be used to block trigger. Lesioning techniques include (*see below* for comparison of techniques):
   A. radiofrequency rhizotomy **(RFR)** (originated by Sweet and Wespic[31]). Uses radiofrequency energy to thermocoagulate the pain fibers. Requires the patient to be awake at intervals during the procedure
   B. glycerol injection into Meckel's cave[32, 33]: possibly lower incidence of sensory loss and anesthesia dolorosa than with radiofrequency lesion[34]. Water soluble contrast cisternography was recommended in original description, may not be essential[35]
   C. mechanotrauma (percutaneous microcompression **(PMC)** rhizolysis): via inflation of No. 4 Fogarty catheter balloon[36-38]. Does not require the patient to be awake
   D. injection of sterile boiling water
4. intradural retrogasserian trigeminal nerve section (sensory portion ± motor root, *see below*): may be performed during MVD if no vascular compression is identified
5. cutting descending trigeminal tract in lower medulla (99.5% success): rarely used
6. microvascular decompression **(MVD)**[39]: (*see below*) microsurgical exploration of root entry zone, usually via posterior fossa craniectomy, and displacement of vessel impinging on nerve (if such a vessel is found). Usually with the placement of a non-absorbable "insulator" (Ivalon® sponge or shredded Teflon felt - see *page 543* for relative merits of Ivalon® vs. Teflon felt)

7. complete section of the nerve proximal to the ganglion via a p-fossa crani
8. stereotactic radiosurgery: *see below*
9. motor cortex stimulation[40]: (somewhat analogous to spinal cord stimulation for spinal or extremity pain). Better for neuropathic trigeminal pain (as distinct from trigeminal neuralgia)

SELECTION OF SURGICAL OPTION

Some pearls that influence treatment option choices (expert opinion[41]):

1. V3 neuralgia: RF. Can selectively treat V3 without involving other divisions
2. V1 or V2: balloon compression. Causes numbness in all 3 divisions, but unlike RF the corneal numbness is better tolerated and the corneal reflex is often preserved
3. bilateral pain: glycerol. It has the shortest duration of effect, which is an advantage if you think you may need to treat the other side at some point
4. SRS: due to latency until pain relief, suboptimal for patients who need immediate pain relief

Peripheral nerve ablation and neurectomies

Limited to pain or trigger points in territory of supraorbital/supratrochlear, infraorbital, or inferior dental nerves. Neurectomy may be a consideration especially for elderly patients who are not candidates for MVD (neurectomy may be done under local anesthesia) with pain in the forehead (to avoid anesthesia of the eye, as could occur with RFR). Disadvantages include sensory loss in the distribution of the nerve and a high rate of pain recurrence due to nerve regeneration (usually in 18-36 months) which often responds to repeat neurectomy[42]. May also be used following PTR.

Supraorbital and supratrochlear nerve: For information on supraorbital neuralgia (SON) or supratrochelar neuralgia (STN), *see page 562*. SON may be treated with rhizotomy (e.g. with alcohol or radiofrequency) or with neurectomy. Alcohol injection is used with caution for STN because of risk of injury to the superior oblique muscle. For neurectomy, these nerves are exposed through a 2 cm incision parallel to and just above the medial portion of the eyebrow (never through the eyebrow as this can create an unsightly “bi-brow”; shaving the eyebrow is also discouraged since it occasionally does not grow back). The incision is carried down to the bone and the periosteum is elevated caudally towards the supraorbital foramen or notch. The nerves will be visible on the

undersurface of the periosteal flap. The supraorbital nerve is freed in its foramen/notch, and is then avulsed by grasping it with a mosquito hemostat and twisting the clamp. The nerve avulses "like pulling a worm out of a hole". The distal portion of the nerve should be located at the site were the periosteum was incised and it, too, should be avulsed. The process can be repeated for the more medially situated supratrochlear nerve.

Other nerves: Not covered here, other nerve branches that may be cut or avulsed include: infratrochlear, lacrimal (the branch of V_1 at the lateral edge of the orbit), infraorbital nerve, inferior alveolar, lingual and mental nerves[43] (p 290).

Percutaneous trigeminal rhizotomy (PTR)

Recommended for patients who: are poor risk for general anesthesia (elderly or those with increased risk for general anesthesia), wish to avoid "major" surgery, have unresectable intracranial tumors, have MS, have impaired hearing on the other side, or have limited life expectancy (< 5 yrs)[34]. For "atypical facial pain", denervating the painful region of the face benefits < 20% of patients, and worsens 20%[44]. Recurrences are easily treated by repeat procedures. May be used to treat failures of peripheral nerve ablation.

Choice of lesion technique:

Recurrence rates and incidence of dysesthesias are comparable among the various lesioning techniques. Incidence of intraoperative hypertension is less with PMC than with radiofrequency rhizotomy **(RFR)** lesion[38] (no reports of intracerebral hemorrhage). Bradycardia occurs regularly with PMC which may not be harmful (some prophylax with atropine[45]). RFR requires a patient who is able to cooperate; PMC can be done with the patient asleep. Paralysis of ipsilateral trigeminal motor root (e.g. pterygoids) is more common after PMC (usually temporary) than RFR, and so PMC should not be done if there is already contralateral paralysis from a previous procedure. See *page 556* for technique.

Microvascular decompression (MVD)

(For more details, *see page 559*).

Recommended for patients with inadequate medical control of pain with > 5 years anticipated survival and able to tolerate a small craniotomy[34] (surgical morbidity increases with age). Relief is often long lived, persevering 10 yrs in 70%. Incidence of facial anesthesia is much less than with PTR, and anesthesia

dolorosa does not occur. Mortality: < 1%. Incidence of aseptic meningitis (AKA hemogenic meningitis): 20%. 1-10% major neurologic morbidity. Failure rate: 20-25%.

1-2% of patients with MS will have a demyelinating plaque at the root entry zone, this usually does not respond to MVD, and one should attempt a PTR.

Stereotactic radiosurgery (SRS)

The first use of SRS by Leksell was for the treatment of TGN. Initially, this was reserved for refractory cases following multiple operations[46], now becoming more widely practiced. The least invasive procedure. Generally recommended for patients with comorbidities, high-risk medical illness, pain refractory to prior surgical procedures, or those on anticoagulants (anticoagulation does not have to be reversed to have SRS).

Treatment plan: 4 -5 mm isocenter in the trigeminal nerve root entry zone identified on MRI. Use 70-80 Gy at the center, keeping the 80% isodose curve outside of the brainstem.

Results: Significant pain reduction after initial SRS: 80-96%[47-50], but only ≈ 65% become pain free. Median latency to pain relief: 3 months (range: 1 d-13 months)[51]. Recurrent pain occurs within three years in 10-25%. Patients with TN and multiple sclerosis are less likely to respond to SRS than those without MS. SRS can be repeated, but only after four months following the original procedure.

Favorable prognosticators: higher radiation doses, previously unoperated patient, absence of atypical pain component, normal pretreatment sensory function[52].

Side effects: Hypesthesia occurred in 20% after initial SRS, and in 32% of those requiring repeat treatment[51] (higher rates associated with higher radiation doses[48]).

MANAGEMENT OF TREATMENT FAILURES

90% of recurrences are in distribution of previously involved divisions; 10% are in new division and may represent progression of the underlying process. Some treatment failures are not persistent TN, but rather represent trigeminal neuropathic pain (AKA trigeminal deafferentation pain).

PTR may be repeated in patients who have a recurrence with some preservation of facial sensation. Attempted repeat PTR is often productive, and failures can be managed as below.

MVD may be performed in patients failing PTR, but the success rate may be reduced[53] (91% for patients undergoing MVD first, vs. 43% for those having MVD following PTR[A]). Repeat MVD may also be performed, with attention given to possible slippage of the insulating sponge, or the fact that the true offending vessel may be “artificially” moved away from the nerve secondary to the surgical positioning.

A. 91% may be an unrealistically high success rate, and taking patients that fail PTR may select for a more difficult subgroup

SRS can be repeated, using the same dose, with reported significant reduction in pain in 89%, and complete relief in 58%[51].

Intradural retrogasserian trigeminal nerve section

May be used as a measure of last resort in patients who have recurrent TGN following one or more PTRs in the presence of total facial anesthesia, or in patients undergoing posterior-fossa craniectomy for the purpose of MVD when no impinging vessel can be identified. In the latter case, a partial rhizotomy is performed by sectioning 2/3 of nerve, with resulting partial anesthesia. In the case of patients with facial anesthesia pre-op, consideration should be given to sectioning the motor division (portio minor) as an alternate pain pathway[11].

PERCUTANEOUS TRIGEMINAL RHIZOTOMY (PTR)

Due to concerns about hemorrhage, check coagulation profile (PT/PTT, consider bleeding time), and discontinue ASA and NSAIDs, preferably 10 days pre-op. Procedure may be performed in OR with fluoro, or in angiography suite in x-ray department.

BOOKING THE CASE - PERCUTANEOUS TRIGEMINAL RHIZOTOMY

BOOKING

(For any of the percutaneous methods: balloon, glycerol, RFR)
Also see defaults & disclaimers (*page v*) and pre-op orders (*see below*).

1. position: supine
2. anesthesia: MAC with sedation
3. equipment:

A. lesion generator and needle kit for radiofrequency rhizotomy
B. C-arm fluoroscopy (2 C-arms for balloon compression)
C. calibrated inflatable balloons (as in kyphoplasty) for balloon rhizotomy

4. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: put a needle into the cheek to numb the nerve to the face
   B. alternatives: medical treatment, surgery through the back of the skull (microvascular decompression), radiation (stereotactic radiosurgery)
   C. complications: facial numbness is anticipated, rarely: stroke, bleeding, blindness

PRE-OP ORDERS (RFR)

1. NPO after MN except meds
2. continue Tegretol® & other meds PO with sips of water
3. AM of procedure: IV NS @ KVO in arm contralateral to neuralgia
4. atropine 0.4 mg IM PRN (✖ contraindications include rapid a-fib)
5. non-disposable LP tray to accompany patient

TECHNIQUE PERCUTANEOUS TRIGEMINAL RADIOFREQUENCY RHIZOTOMY ***(RFR)***

Adapted technique[54]. NB: needle insertion and/or lesioning may cause HTN, consider monitoring BP. Use either a straight electrode (bare 5 mm for 1 division, 7.5 mm for 2 divisions, or 10 mm for total lesions) or a curved electrode[55].

Electrode insertion

1. attach ground electrode to patient's upper arm
2. prep the cheek on the involved side with Betadine
3. entry point: under short-acting anesthetic agent (e.g. propofol (Diprivan® - *see page 24*) or methohexital (Brevitol® - *see page 24*), insert electrode-needle **2.5-3 cm lateral to oral commissure**
4. trajectory:
   A. palpate the buccal mucosa with a gloved finger inside the mouth (lateral to the teeth) and with the other hand pass the electrode medial to the coronoid process of the mandible (keeping the needle deep to the oral mucosa, i.e. outside the oral cavity) initially aiming towards the plane intersecting a point **3 cm anterior to EAM** and the **medial**

aspect of the pupil when the eye is directed forward. Be careful not to contaminate the field with the hand that was in the patient's mouth

B. as insertion progresses, use fluoroscopy to direct the tip towards the intersection of the top of the petrous bone with the clivus (5-10 mm below floor of sella along clivus)

C. upon entering foramen ovale the masseter often contracts, causing the jaw to briefly close. Remove the stylet, look for CSF to verify location (may not occur in re-do cases), and insert electrode through needle

In difficult cases, intraoperative fluoroscopy may assist in localizing the needle to Meckel's cave and to R/O e.g. entry into superior orbital fissure (which can cause blindness after lesioning), or entry into foramen spinosum (middle meningeal artery). If necessary to visualize (e.g. when there is difficulty entering), the foramen ovale is optimally seen on a submental x-ray by hyperextending neck 20° and rotating head 15-20° away from side of pain[56].

Impedance measurements: from the tip of the electrode when available may help indicate location of needle tip. Impedance: CSF (or any fluid) low (≈ 40-120 Ω); connective tissue, muscle, or nerve is usually 200-300 Ω (may be up to 400 Ω); if > 400 Ω this likely indicates electrode is contacting periosteum or bone. After starting the lesion, impedance often goes down by 30 Ω transiently, and then as the lesioning continues it gradually returns to baseline or ≈ 20 Ω above it. If char develops on the electrode tip, the impedance will read higher than where it started.

Stimulation and repositioning

Once the foramen ovale is entered, the needle is positioned with the following guidelines: for V3 division lesion the curved electrode should be just short of the clivus and pointing down, for V2 it is at the clivus and directed up, for V1 it is 5 mm beyond clivus and pointing up. ✖ At no time should the needle tip extend > 8 mm beyond clival line (to avoid Cr. N. III or VI complications).

The patient is allowed to wake up and is stimulated through the electrode with the following settings: frequency = 50-75 Hz, 1 mS duration, start at 0.1 V amplitude and slowly increase (usually 0.2-0.5 V is adequate, higher voltages may indicate that the needle is not near the target and that stimulation is due to far-field currents, however, in previously lesioned patients up to 4 V may sometimes be necessary). If stimulation does not reproduce pain in the distribution of the patient's TGN, then the amplitude is returned to 0, the electrode is repositioned (straight electrode: advance needle < 5 mm at a time,

until the tip is in the vicinity of the clival line; curved tip electrode: advance and/or rotate) and then slowly elevate the voltage again from 0 and repeat the repositioning-stimulating process until stimulation reproduces the distribution of tic pain. If previous lesions have produced analgesia and the patient cannot feel the stimulating current, one may stimulate at 2 Hz. and watch for masseter twitch (requires preserved motor root).

Lesioning

When stimulation produces pain in the involved distribution of the TGN, perform the first lesion under short-acting anesthesia at 60-70° C **x** 90 sec. A facial flush may be noted[56]. After every lesion, perform a post-lesion assessment (*see below*). The goal is analgesia (but not anesthesia) in the areas of tic pain and hypalgesia in areas of trigger points. An average of three lesions are necessary at the first sitting, each ≈ 5° C higher than the previous for 90 seconds. Anesthetic may not be needed after the first lesion if moderate analgesia has been produced by previous lesions.

Post-lesion assessment

After each lesion and at completion of procedure, assess:

1. sensitivity to pinprick and light touch in all three divisions of trigeminal nerve (grading: normal, hypalgesic, analgesic, anesthetic)
2. corneal reflex bilaterally
3. EOM function
4. masseter muscle strength (patient clenches teeth, palpate cheeks for contraction)
5. pterygoid muscle strength (ask patient to open mouth, chin deviates towards side of pterygoid weakness)

Post-op care (PTR)

Include in post-op orders:

1. ice pack to face on side of procedure for 4 hrs
2. soft diet
3. routine activity when alert
4. avoid narcotics (usually not necessary)
5. if corneal reflex impaired: risk of neuroparalytic keratitis. Natural tears 2 gtt q 2 hrs while awake to eye on affected side. Lacrilube® to eye & tape

eye shut q hs

Prior to discharge from hospital, repeat post-lesion assessment (*see above*). Patients are then weaned off of carbamazepine as tolerated.

PERCUTANEOUS MICROCOMPRESSION RHIZOLYSIS BALLOON (PMC)

Via inflation of No. 4 Fogarty catheter balloon.

Technique

1. the needle is placed as with RFR (*see page 556*).
2. aim for balloon placement in the medial foramen ovale (to avoid entering the middle fossa). After placing the balloon, insert the stylet to visualize where the balloon will go. Use Omnipaque 240 to fill the balloon
3. inflate to 1.4 atmospheres of pressure

COMPLICATIONS[A]

1. mortality: only 17 deaths in over 22,000 procedures (includes lesser experienced neurosurgeons and patients often considered poor surgical risks)[21]
2. dysesthesias[24] (sometimes called "annoying paresthesias"): higher rate in more complete lesions
   A. minor: 9%
   B. major (requiring medical treatment): 2%
   C. **anesthesia dolorosa** (severe, constant, burning aching pain that is refractory to all treatment): 0.2-4%
3. meningitis[23]: 0.3%
4. alterations in salivation[57]: 20% (increased in 17%, decreased in 3%)

	------850 cases[55]------		315 cases[57]
	straight electrode (N = 700)	curved electrode (N = 150)	
5. partial masseter weakness (usually not perceived by patient)	15-24%	7%	50%
6. oculomotor paresis (usually temporary)	2%	0	
7. reduced hearing (secondary to paresis of tensor tympani)	0	0	27%
8. **neuroparalytic keratitis** (keratitis due to fifth nerve deficit which impairs sensation)	4%	2%	0

9. intracranial hemorrhage: personal report of 7 cases (6 fatal) in > 14,000 procedures, probably due to transient HTN (SBP up to 300 torr)
10. alterations in lacrimation[57]: 20% (increased in 17%, decreased in 3%)
11. herpes simplex eruption: prescribe antiherpetic drug if patient develops symptoms (e.g. Acyclovir® - *see page 360*)
12. bradycardia and hypotension: 1% with RFR, up to 15% with glycerol injection
13. rare[58, 59]:
    A. temporal lobe abscess
    B. intracerebral abscess: 0.1%
    C. aseptic meningitis
    D. trigeminal trophic syndrome **(TTS)**[60]: triad of unilateral crescentic nasal alar ulceration with anesthesia and paresthesia of the trigeminal dermatome (may present with severe pruritus and self-induced skin lesions from scratching). A result of trigeminal nerve injury. Treatment has included: carbamazepine, diazepam, amitriptyline, chlorpromazine, clonazepam or pimozide[61]
    E. complications related to needle placement[62]:
        1. carotid cavernous fistula **(CCF)**: may occur with any percutaneous technique[63] (including balloon microcompression[64])
        2. injury to other cranial nerves: II, III, IV, VI[65]
        3. blindness: from penetration of inferior orbital fissure[66]
    F. subarachnoid hemorrhage
    G. seizures

A. NB: some “numbness” is actually expected in most successful PTRs and occurs in 98% of cases[24], and is not considered a complication here

Table 20-3 Comparison of outcomes of percutaneous techniques to MVD

Parameter	Percutaneous techniques (PTR)			MVD
	RFR*	Glycerol	Balloon	
initial success rate[11, 24]	91-99%	91%	93%	85-98%
medium-term recurrence rate	19% at 6 yrs[23]	54% at 4 yrs	21% at 2 yrs	15% in 5 yrs
long-term recurrence rate	80% at 12 yrs[57] †			30% at 10 yrs
facial numbness[24]	98%	60%	72%	2%

* abbreviations: RFR = radiofrequency rhizotomy; MVD = microvascular decompression; balloon = balloon microcompression

† this author included initial failures to PTR requiring repeat procedures during same hospitalization

Results (PTR)

Results of various PTR techniques compared to microvascular decompression **(MVD)** are shown in *Table 20-3*. Recurrence rate is higher in patients with multiple sclerosis (50% at 3 yrs mean F/U)[67].

MICROVASCULAR DECOMPRESSION (MVD) FOR TRIGEMINAL NEURALGIA

Indications:

1. patients unable to achieve adequate medical control of trigeminal neuralgia with ≥ 5 yrs anticipated survival, without significant medical or surgical risk factors[34] (although a small p-fossa exploration is usually well tolerated, surgical morbidity increases with age)
2. may be used in patients who do not fit the above criteria, but have intractable pain and fail PTR
3. patient with tic involving V1 for whom the risk of exposure keratitis due to corneal anesthesia would be unacceptable (e.g. already blind in contralateral eye) or patient wishing to avoid facial anesthesia for any reason

✖ patients with MS are usually not considered candidates for MVD due to low response rate

Booking the case - microvascular decompression

Also see defaults & disclaimers (*page v*) and pre-op preparation (*see below*).

1. position: park bench
2. equipment: microscope
3. implants: Ivalon sponge or shredded Teflon
4. intra-op monitoring: (optional) BAER, possible nervus intermedius
5. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery behind the ear to move a blood vessel from the sensory nerve of the face, if no offending vessel can be identified then possible partial sectioning of the appropriate part of the trigeminal nerve with associated numbness)
   B. alternatives: needle procedures through the cheek (percutaneous rhizotomy), radiation (stereotactic radiosurgery)
   C. complications: (in addition to usual craniotomy complications), CSF leak, hearing loss, facial numbness, pain near incision (occipital neuralgia or lesser occipital neuralgia), rarely: diplopia, facial paralysis, failure of the procedure

Technique

Also see *Paramedian suboccipital craniectomy*, page 154 for important pointers, including use of armored endotracheal tube.

Preoperative preparation

An MRI is recommended to rule-out mass lesion or vascular abnormality. Baseline BAER are performed by some[68] (*see below* for intra-op monitoring).

O.R. setup

Setup for lateral oblique suboccipital (posterior-fossa) craniotomy (*see page 154*). Microscope: observer's eyepiece is placed on the side opposite to that of the tic.

Positioning[69]

- lateral oblique position (*see page 154*), symptomatic side up, axillary roll
- thorax elevated 10-15° to reduce venous pressure

- 3-pin skull fixation. Head position:
  - ♦ head rotation: head rotated just slightly away from the affected side
  - ♦ lateral head tilt
    - for trigeminal neuralgia or VIII nerve approach: the head is parallel to the floor (if it is lower, nerves VII & VIII will obscure view of V)
    - for VII nerve or lower, the vertex is tilted 15° <u>down</u> from the horizontal
  - ♦ flex neck: leave 2 fingerbreadths room between the chin and the sternum
- upper shoulder retracted caudally with adhesive tape
- option: lumbar spinal drain. Drain 20-30 cc during craniotomy, then drain off small amounts from time-to-time during the case to keep the field mostly dry, but occasionally letting CSF build up to bathe cranial nerves

Intra-operative monitoring

Option: intraoperative monitoring of facial EMG and BAER (assesses acoustic nerve)[68].

Approach

1. skin incision[69]: vertical incision 3-5 cm in length, 5 mm medial to mastoid notch (a small "5-6-4" incision - *see page 155*) (in thick or short-necked patients, a slightly longer incision that angles inferomedially is used). 75% of the incision is inferior to the transverse sinus, 25% superior
2. burr hole:
   A. 1 cm inferior and 1 cm medial to the asterion[70] pp 60
   B. if the asterion is not easily identified or if there are concerns about the reliability of the asterion as a landmark for the junction of the transverse and sigmoid sinuses[71], place the burr hole directly over the mastoid emissary vein which drains superolaterally into the sigmoid sinus
3. craniotomy: top of bone opening as close as possible to transverse sinus. The position of the **transverse sinus** can be approximated by a line drawn from the posterior base of the zygomatic process to the inion, or roughly ≈ 2 finger-breadths above the upper end of the mastoid notch. Lateral limit of bone opening is sigmoid sinus. A triangular bony opening with a leg along each sinus works well. Craniectomy diameter needs to be only ≈ 3

cm. Apply bone wax liberally (blocks off any possible opening into the mastoid air cells)

4. dural opening: either a curvilinear with each end at a sinus and the convexity away from the junction (Jannetta) or an inverted "T" (with one incision towards each sinus and the third towards junction of sinuses)

Technique

- minimal or no retraction of cerebellum is usually required
- allow CSF to drain before proceeding: this may require gentle advancement of a cottonoid in the CPA. A lumbar drain should be placed if CSF cannot be drained
- follow the junction of tentorium with temporal bone deep. Place a retractor that both medially displaces the cerebellum and slightly "lifts" the cerebellum towards the surgeon (medial displacement alone is not as effective)
- petrosal vein: coagulate and divide the petrosal vein complex (usually 2-3 veins connecting to the tentorial dura). If the vein is torn, the dural side is tamponaded (sometimes up to 30 minutes is needed) while the free end is coagulated
- V is deeper than the VII/VIII complex, which should not even be seen with this approach. If VII/VIII are seen, move the retractor superiorly as even gentle traction may cause hearing loss (see *Figure 5-8*, page 90). There is often a hillock of bone just posterior to Meckel's cave obscuring the site where the fifth nerve enters the cave
- arachnoid overlying the fifth nerve is sharply divided (caution re Cranial Nerve IV which follows the tentorial opening in the arachnoid rostral to the fifth nerve). Intra-op changes in BAER are often attributed to retraction of arachnoid that is tethered to the VII/VIII complex
- the fifth nerve may be markedly atrophic if previous PTRs have been done
- identify the smaller motor root (portio minor) of the fifth nerve
- arteries and/or veins compressing V should be dissected off the nerve. NB: vessels located proximally are the most likely offenders, however, the dorsal root entry zone (which is the sensitive part of the nerve) may be variable in location and peripheral vessels may be culpable. The nerve should be inspected and freed of vessels from its origin at the brainstem all the way to its entrance into Meckel's cave[69]. Veins may be coagulated and then should be divided (to prevent recanalization)

- the most common cause of compression is the superior cerebellar artery **(SCA)**
- check the nerve at the junction with brainstem for any residual compression prior to the next step
- insulating material is interposed between nerve and vessel to prevent re-compression. Options include:
  - e.g. Ivalon®, (polyvinyl formyl alcohol) sponge (Ivalon Surgical Products, 1040 OCL Parkway, Eudora, KS, 66025, U.S.A. distributed by Fabco in the U.S.A. (860) 536-8499, toll free: (888) 813-8214, http://www.fabcousa.net) cut in a saddle shape. Note: if an Ivalon block is used instead of pre-packaged sterile pads, it must be rinsed thoroughly to remove formalin, then autoclaved. Ivalon should be hydrated in NS for 10 minutes prior to cutting it
  - shredded Teflon felt (see *page 543* for merits of Ivalon® vs. Teflon or muscle)
- Wilson recommends performing a partial sensory rhizotomy of the inferior one-half to two-thirds of the portio major for the following: cases where no vascular contact with the nerve or no deformity of the nerve is identified, in most cases of patients undergoing a repeat MVD, or for cases with duration of symptoms > 8-9 yrs as this latter group tends to have a lower success rate with MVD alone[72]
- if the procedure is for a failed MVD and it is desired to partially divide the nerve, the nerve is organized somatotopically with V1 fibers superiorly, and V3 inferiorly. If the goal is total elimination of pain pathways and there is concern about pain conduction through ancillary pathways, consider also dividing the motor root (portio minor)

Closure

- bone wax should be applied liberally to the exposed lateral bone edges (to paraphrase Dr. Jannetta[69] and Mr. Miyagi[73], "Wax in, wax out.")
- irrigate gently with warm saline (avoid "jet" irrigation which can damage the VIII nerve)
- intra-op BAER decline may occur on dural closure and should prompt reopening of the dura and checking for tension on the VIII nerve from a vessel or Telfa
- perform several Valsalva maneuvers to ensure watertight closure of dura
- the bone defect should be covered e.g. with burr hole cover to reduce

chance of pain associated with uncovered craniectomy

- after fascial closure, Valsalva maneuver is performed again to ensure watertight closure
- use 4-0 running locked nylon to approximate skin in watertight fashion (avoid excessive tension)

Post-op care following MVD

Include in post-op orders

1. admit to ICU
2. arterial-line for continuous BP monitoring
3. analgesics (e.g. codeine 30-60 mg IM q 3 hrs)
4. anti-emetics (e.g. ondansetron 4 mg IV q 6 hrs)
5. medication to aggressively treat HTN (viz. SBP > 160 mm Hg)

Post-op H/A, nausea and pain

Patients routinely have H/A and nausea for 2-3 days (there tends to be less intracranial air and less "pneumoencephalogram sickness" if the park-bench position is used instead of the sitting position). However, severe H/A should prompt a STAT CT to R/O bleeding. If the CT is negative, severe H/A may be due to transient elevation of CSF pressure that occurs in some, and which usually responds to 1, or at most 2, LPs to halve the pressure. Aseptic meningitis usually responds to steroids. Some patients have continued but lessened tic douloureux pain for several days post-op, this usually subsides[69].

Complications

The short list:

1. cerebellar injury
2. hearing loss
3. CSF leak

The long list:

1. mortality: 0.22-2% in experienced hands (> 900 procedures)[74, 75]
2. meningitis
   A. aseptic meningitis (AKA hemogenic meningitis): H/A, meningismus, mild fever, culture negative CSF, pleocytosis. Incidence: ≈ 2% (up to

20% has been reported). Usually occurs 3-7 days post-op. Responds to LP + steroids

B. bacterial meningitis: 0.9%

3. major neurologic morbidity: 1-10% (higher rates with less experienced surgeons), including:

A. deafness: 1%

B. vestibular nerve dysfunction

C. facial nerve dysfunction

4. mild facial sensory loss: 25%
5. cranial nerve palsies[76]:
   - A. fourth nerve (diplopia): 4.3% (only ≈ 0.1% are permanent)
   - B. facial nerve: 1.6% (most are transient)
   - C. eighth nerve (hearing loss): 3%
6. postoperative hemorrhage[77]: subdural, intracerebral (1%[24]), subarachnoid
7. seizures: including status epilepticus[77]
8. infarction[77]: including posterior cerebral artery distribution, brain stem
9. CSF leak: resolves with lumbar drainage in most cases
10. pneumonia: 0.6%

OUTCOME

1. success rate[A]: 75-80%; good but not total relief in an additional ≈ 10%
2. recurrence rate in large series is difficult to ascertain from literature; in a series of 40 patients followed 8.5 yrs mean[75]:
   - A. major recurrence (recurrent tic not controlled by medications) rate: 31%
   - B. minor recurrence (mild or controlled by medications) rate: 17%
   - C. using Kaplan-Meier curve, expect 70% to be either pain free or have minor recurrence by 8.5 years (or ≈ 80% at 5 years)
     the risk for a <u>major</u> recurrence after MVD is 3.5% annually
     the risk for a <u>minor</u> recurrence after MVD is 1.5% annually
   - D. major recurrence rate is lower for patients having major arterial cross-compression of the nerve discovered at the time of surgery (patients with venous compression had much higher rate)
   - E. this study found no correlation between previous destructive surgery and major recurrence rate (in 11 patients)

A. rates may be lower in patients having prior destructive procedure, see *Management of treatment failures*, page 555

Some feel that the longer one waits before performing a MVD, the lower the success rate.

20.2.2. Supraorbital and supratrochlear neuralgia

Anatomy

The supraorbital and supratrochlear nerves arise from the frontal nerve and are 2 of the 5 branches of V_1 (ophthalmic division of the trigeminal nerve). The supraorbital nerve is the largest branch. It exits the orbit through the supraorbital notch or foramen, usually within the medial third of the orbital roof (mean distance from exit to medial angle of orbit: 20 mm (range: 5-47)[78]). The supratrochlear nerve exits the orbit without a foramen or notch 3-38 mm medial to the supraorbital nerve (mean: 15.3 mm)[78]), the most medial branch varies from 8-30 mm lateral to the patient's midline[78].

Supraorbital neuralgia characteristics

Trigeminal neuralgia (TGN) may present with pain in the distribution of the supraorbital nerve, however, the supraorbital nerve may be involved in supraorbital neuralgia **(SON)**, a distinct syndrome with different clinical characteristics. SON is a rare condition slightly more common in women, with onset typically 40-50 years of age[79]. Characteristics[80]: 1) unilateral pain in the distribution of the supraorbital nerve (see *Figure 7-2*, page 151), 2) tenderness in the region of the supraorbital notch or along the distribution of the nerve, and 3) temporary relief with nerve block.

The pain is usually chronic-continuous or remitting-intermittent[79].

SON may be:

1. primary (no identifiable etiology): these cases lack any sensory loss
2. secondary (e.g. due to trauma to the area, or resulting from chronic pressure such as with wearing swim goggles): more common than primary SON. Most cases remit within one year[79] with elimination of the offending

pressure

Supratrochlear neuralgia

Cases of pain isolated to the supratrochlear nerve appear to exist. Supratrochlear neuralgia **(STN)** may be differentiated from SON by restriction of pain in the more medial forehead, and with relief on blockade of the supratrochlear nerve alone.

Differential diagnosis

1. migraine: suggested by nausea, vomiting and photophobia
2. associated autonomic activity is rare with SON, and should prompt consideration of cluster H/A (*see page 58*) or SUNCT (*page 549*)
3. TGN: typical TGN features <u>lacking</u> in SON include characteristic triggers and pain consisting exclusively of paroxysmal/ultra-brief electric shock-like pain
4. hemicrania continua: continuous unilateral pain that tends to be located more posteriorly and is absolutely responsive to indomethacin[80]
5. trochleitis: inflammation of the trochlea/superior-oblique muscle complex, may mimic supratrochlear neuralgia with pain of the medial upper orbit extending a short distance to the forehead[81]. The pain is typically exacerbated by supraduction of the eye and to palpation of the trochlea, and is relieved with injection of local anesthetic or, by the usually definitive treatment of infiltration of corticosteroids close to the trochlea. Diplopia is rare and minimal
6. numular (coin-like) H/A82: round or oval 2-6 cm diameter area of pressure-like continuous head pain without underlying structural abnormality. In 13 patients, 9 (70%) the area was located at the parieto-occipital junction. 9 (70%) demonstrated hypoesthesia and touch provoked paresthesias in the affected area

Treatment

Gabapentin (800-2400 mg/d) or pregabalin (150 mg/d) is helpful for some[83].

Topical capsaicin applied to the symptomatic area may help (*see page 553*).

Refractory cases may respond to rhizotomy with alcohol (providing an average of 8.5 months relief[84]) or with radiofrequency ablation.

Persistent cases may require exploration and decompression of the nerve by

lysing bands overlying the supraorbital notch[85], or, ultimately, to neurectomy (*see page 554*) which provides an average of 33.2 months relief[86].

20.2.3. Glossopharyngeal neuralgia

Incidence: 1 case for every 70 of trigeminal neuralgia[87] (p 3604-5).

CLINICAL

Severe, lancinating pain in the distribution of the glossopharyngeal and vagus nerves (throat & base of tongue most commonly involved, radiates to ear (otalgia), occasionally to neck), occasionally with salivation and coughing. Rarely: hypotension[88], syncope[89], cardiac arrest and convulsions may accompany. May be triggered by swallowing, talking, chewing. Trigger zones are rare.

TREATMENT

Pain may be reduced by cocainization of tonsillar pillars and fossa. Usually, the persistence and severity of pain requires surgical intervention. One may either perform microvascular decompression, or nerve division via extra- or intracranial approach (latter may be required for permanent relief).

Intracranial approach: Section of preganglionic glossopharyngeal nerve (IX) and upper one third or two fibers (whichever is larger) of vagus (X). IX is readily identified at it's dural exit zone where it is separated from X by a dural septum. The upper third of X is usually composed of a single rootlet, or less commonly, multiple small rootlets. Initial post-op dysphagia usually resolves. Cardiovascular complications following vagal section have been reported, warrants close monitoring **x** 24 hrs.

20.2.4. Geniculate neuralgia

Geniculate neuralgia **(GeN)** AKA **Hunt's neuralgia** AKA nervus intermedius neuralgia: a very rare neuralgia affecting the nervus intermedius (the somatic sensory branch of the facial nerve primarily innervating mechanoreceptors of the hair follicles on the inner surface of the pinna and deep mechanoreceptors of nasal and buccal cavities and chemoreceptors in the taste buds on the anterior 2/3 of the tongue).

Symptoms: unilateral paroxysmal otalgia (lancinating pain experienced deep within the ear, often described as an “ice pick in the ear”) radiating to the auricle, with occasional burning sensations around the ipsilateral eye and cheek, and **prosopalgia** (pain referred to deep facial structures, including orbit, posterior nasal and palatal regions). During pain attacks, some patients have: salivation, bitter taste, tinnitus, or vertigo.

GeN occasionally has cutaneous trigger points in the anterior EAC and tragus, and pain may also be triggered by cold, noise, or swallowing.

Work-up includes neuro-otologic evaluation with audiometry and ENG. Some patients may require imaging (MRI or high-resolution CT) and angio (to R/O aneurysm).

Variants

Tic convulsif (AKA convulsive tic): GeN combined with hemifacial spasm, usually due to neurovascular compression of both the sensory and motor roots of the facial nerve[17], most often by AICA. First described by Cushing in 1920.

GeN may be associated with herpetic infections of the geniculate ganglion (AKA **herpetic ganglionitis**, AKA **Ramsay Hunt syndrome (RHS)**) in which case herpetic lesions appear on pinna, in EAC, and possibly on TM. May include facial palsy, decreased auditory acuity, tinnitus or vertigo. Unlike idiopathic GeN, RHS is more chronic and less paroxysmal, tends to remit with time, and is usually refractory to carbamazepine. Idiopathic GeN tends to be more painful than RHS, and does not remit spontaneously.

Treatment

1. medical therapy
   A. mild cases may respond to carbamazepine, sometimes in combination with phenytoin
   B. may respond to valproate (Depakote®) 250 mg PO BID
   C. topical antibiotics for secondary infections of herpetic lesions
   D. local anesthetic to EAC
2. surgery: for severe cases where medical treatment fails or is not tolerated
   A. microvascular decompression together with division of the nervus intermedius (nerve of Wrisberg[90]). Operating under local anesthesia allows verification by stimulating nerve

B. geniculate ganglion section[91]

20.3. Postherpetic neuralgia

Herpes zoster (HZ) (Greek: *zoster* - girdle) (**shingles** in lay terms): painful vesicular cutaneous eruptions caused by the herpes varicella zoster virus **(VZV)** (the etiologic agent of chickenpox, a herpesvirus distinct from herpes simplex virus). It occurs in a dermatomal distribution over one side of the thorax in ≈ 65% of cases (rarely, infections occur without vesicles, called **zoster sine herpete**). In 20% of cases it involves the trigeminal nerve (with a predilection for the ophthalmic division, called **herpes zoster ophthalmicus**). Pain usually resolves after 2-4 weeks. When the pain persists > 1 month after the vesicular eruption has healed, this pain syndrome is known as **postherpetic neuralgia (PHN)**. PHN can follow a herpes varicella infection in any site and is difficult to treat by any means (medical or surgical). It can occasionally be seen in a limb, and follows a dermatomal distribution (not a peripheral nerve distribution). PHN may remit spontaneously, but if it hasn't done so by 6 mos this is unlikely.

EPIDEMIOLOGY

Incidence of herpes zoster is ≈ 125/100,000/year in the general population, or about 850,000 cases per year in the U.S.[92]. Both sexes are equally affected. There is no seasonal variance. HZ is also more common in those with reduced immunity and in those with a coexistent malignancy (especially lymphoproliferative)[93, 94]. PHN occurs in ≈ 10% of cases of HZ[92]. Both HZ and PHN are more common in older patients (PHN is rare in age < 40 yrs, and usually occurs in age > 60) and in those with diabetes mellitus. PHN is more likely after ophthalmic HZ than after spinal segmental involvement.

ETIOLOGY

It is postulated that the VZV lies dormant in the sensory ganglia (dorsal root ganglia of the spine, trigeminal (semilunar) ganglion for facial involvement) until such time that the patient's immune system is weakened and then the virus erupts. Inflammatory changes within the nerve are present early and are later replaced by fibrosis.

CLINICAL

PHN is usually described as a constant burning and aching. There may be superimposed shocks or jabs. It rarely produces throbbing or cramping pain. Pain may be spontaneous, or may be triggered by light cutaneous stimulation (allodynia) (e.g. by clothing), and may be relieved by constant pressure. The pain is present to some degree at all times with no pain-free intervals. Scars and pigmentary changes from the acute vesicular eruption are usually visible. It is not known if PHN can follow zoster sine herpete. The involved area may demonstrate hypesthesia, hypalgesia, paresthesias and dysesthesias.

Table 20-4 Medical treatments for PHN*

Treatment	Efficacy
PHN treatments that appear effective	
tricyclic antidepressants	widely used(*see text*)
lidocaine patch (Lidoderm®) 95	effective, few side effects (*see page 566*)
intrathecal steroids + lidocaine (*see text*)	appears very effective, larger studies & long-term follow-up needed
gabapentin	proven efficacy (*see text*)
oxycodone CR 10 mg PO BID4	proven efficacy
Treatments of questionable efficacy	
SSRIs[†]	may be effective
SNRIs	may be effective
tramadol	may be effective
topical capsaicin	controversial (*see text*)
iontophoresis	insufficient evidence
nonsteroidal creams	questionable
aspirin suspended in acetone, ether or chloroform	questionable
EMLA cream	questionable
Treatments that are not useful	
dextromethorphan, benzodiazepines, acyclovir, acupuncture	no benefit[96]
ketamine (NMDA receptor antagonist)	may be beneficial, but hepatotoxic
Preventative treatment	
oral antiherpetic drugs given during HZ infection	shortens length of HZ, may reduce incidence of PHN
varicella vaccination of older patients	trials of this strategy are in progress[92]

* modified with permission from Rubin M, Relief for postherpetic neuralgia, **Neurology Alert**, 6: 33-4, 2001

† abbreviations: oxycodone CR = controlled release (Oxycontint®); HZ = herpes zoster; PHN = postherpetic neuralgia; SNRIs = serotonin-norepinephrine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors (e.g. Prosac®),

MEDICAL TREATMENT

Varicella vaccination of older individuals can increase immunity to herpes zoster, but it will be several years before it can be determined if this will reduce PHN[92].

FOR HERPES ZOSTER

Treatment for the pain of the acute attack of herpes zoster may be accomplished with epidural or paravertebral somatic (intercostal) nerve block[97 (p 4018)].

Oral antiherpetic drugs: Also effective (they shorten the duration of pain) and also reduce the incidence of PHN. They may cause thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) when used in severely immunocompromised patients at high doses. These drugs include:

Acyclovir (Zovirax®): poorly absorbed from the GI tract (15-30% bioavailability). ***Rx*** 800 mg PO q 4 hrs 5 times/d **x** 7 d.

Valacyclovir (Valtrex®)[98] is a pro-drug of acyclovir and is more completely absorbed and should be equally as effective with fewer daily doses. ***Rx*** 1,000 mg PO TID starting within 72 hrs of onset of the rash **x** 7 days.

Famciclovir (Famvir®): ***Rx*** 500 mg PO TID **x** 7 d.

FOR POST-HERPETIC NEURALGIA

Most drugs useful for trigeminal neuralgia (*see page 552*) are less effective for PHN. Some treatment alternatives for PHN are summarized in *Table 20-4*. Details of some drugs follows. It is suggested to initiate therapy with lidocaine skin patches (*see page 566*) since this modality has the lowest potential for serious side effects[92].

Antiepileptic drugs

gabapentin (Neurontin®) **DRUG INFO**

FDA approved only for partial seizures and postherpetic neuralgia **(PHN)**.

SIDE EFFECTS: dizziness and somnolence (usually during titration, often diminish with time). Ataxia, fatigue, peripheral edema, confusion and depression may occur.

Rx For PHN, start with 300 mg on Day 1, 300 mg BID on Day 2, and 300 mg TID on Day 3. Dose may be titrated up to 1800 mg/d divided TID. To limit daytime drowsiness, patients may need to start with 100 mg at hs and increase slowly over 3-8. Although doses up to 3600 mg/day (the antiseizure dose) were studied[99] there was no significant benefit for PHN over 1800 mg/d. Lower doses are required for renal insufficiency. **SUPPLIED**: 100, 300 & 400 mg capsules; 600 & 800 mg scored tabs. 50 mg/ml suspension.

oxcarbazepine (Trileptal®) DRUG INFO

Rx 150 mg PO BID.

zonisamide (Zonegran®) DRUG INFO

Rx Initiate therapy with 100 mg PO q PM **x** 2 wks, then increase dose by 100 mg/d q 2 wks up to 400 mg/d. Bioavailability is not affected by food. Steady state is achieved within 14 days of dosage changes. **SUPPLIED**: 100 mg capsules.

Tricyclic antidepressants (TCA):

For side effects *see page 797*.

amitriptyline (Elavil®) DRUG INFO

Helpful in ≈ 66% of patients at a mean dose of 75 mg/d even without antidepressant effect[5]. **SIDE EFFECTS:** (see *Amitriptyline, side effects* page 797), minimized by starting low and slowly incrementing dose.

Rx Start with 12.5-25 mg PO q hs, and increase q 2-5 days to a max of 150 mg/d.

nortriptyline (Pamelor®) DRUG INFO

Fewer side effects than amitriptyline.

Rx Start with 10-20 mg PO q hs, and increase gradually to a max of 150 mg/d.

Topical treatment:

capsaicin (Zostrix®) DRUG INFO

A vanillyl alkaloid derived from hot peppers, available without prescription for topical treatment of the pain of herpes zoster and diabetic neuropathy. Beneficial in some patients with either of these conditions (response rate at 8 weeks was 90% for PHN, 71% for diabetic neuropathy, vs. 50% with placebo in either group), although the high placebo response rate is disturbing and many authorities are skeptical[100]. Expensive. **SIDE EFFECTS:** include burning and erythema at the application site (usually subsides by 2-4 weeks).

Rx Manufacturer recommends massaging the medication into the affected area of the skin TID-QID (apply a very thin coat). Some authorities recommend q 2 hr application. Avoid contact with eyes or damaged skin. Supplied as Zostrix® (0.25% capsaicin) or Zostrix-HP® (0.75%).

lidocaine patch 5% (Lidoderm®) DRUG INFO

Often better tolerated by elderly patients than TCAs (due to pre-existing cognitive impairments, cardiac disease, or systemic illness).

Rx Apply up to 3 patches of 5% lidocaine (to cover a maximum of 420 cm^2) to intact skin q 12 hrs to cover as much of the area of greatest pain as possible[95].

Intrathecal steroids

Over 90% of patients receiving intrathecal methylprednisolone (60 mg) + 3% lidocaine (3 ml) given once per week for up to 4 weeks, reported good to excellent pain relief for up to 2 years[101]. This technique was not studied for use

in PHN involving the trigeminal nerve. Further clinical trials are needed to verify the efficacy and safety[92] (potential long-term side effects include adhesive arachnoiditis).

SURGICAL TREATMENT

There is no operation that is uniformly successful in treating PHN. Numerous operations have been shown to work occasionally. Procedures that have been tried include:

1. nerve blocks: once PHN is established, nerve blocks provide only temporary relief[102]
2. cordotomy: although percutaneous cordotomy (*see page 568*) may work when the level of PHN is at least 3-4 segments below the cordotomy, this procedure is not recommended for pain of benign etiology because of possible complications and the high likelihood of pain recurrence
3. rhizotomy: including retrogasserian for facial involvement
4. neurectomies
5. sympathectomy
6. DREZ[103]: often offers good early relief, but recurrence rate is high (*see page 575*).
7. acupuncture[104]
8. TENS
9. spinal cord stimulation: *see page 572*
10. undermining the skin
11. motor cortex stimulation: for facial PHN

20.4. Pain procedures

Medical therapy must be maximized before a patient is a candidate for a pain procedure. Usually this requires escalating the dose of oral narcotic pain medications until the point that the pain is relieved or the side effects (usually somnolence or hallucinations) are intolerable (e.g. up to 300-400 mg/day of MS Contin may sometimes be necessary).

Choice of pain procedure: *Table 20-5* shows some pain procedures that may be used for various indications. In general, nonablative procedures are exhausted before resorting to ablative procedures.

Table 20-5 Choice of pain procedures*

Unilateral pain		Bilateral or midline pain	
Head, face, neck, UE	Pain at or below C5 dermatome	Below diaphragm	Above diaphragm
DBS	cordotomy † (568)	spinal IT narcotics (570) ↓ commissural myelotomy (570)	intraventricular narcotics (572)
stereotactic mesencephalotomy (567)			

* abbreviations: IT = intrathecal, UE or LE = upper or lower extremity, numbers in parentheses = page

† cordotomy (open or percutaneous) if pain is unresponsive to or too high for spinal IT narcotics

Types of pain procedures

For pain procedures particular to trigeminal neuralgia, *see page 553*. Techniques for other conditions include:

1. electrical stimulation
   A. deep brain stimulation[105]: targets include thalamus and periaqueductal or periventricular gray matter (*see page 574*)
   B. spinal cord stimulation: *see page 572*
2. direct drug administration into the CNS:
   A. different routes: spinal (*see page 570*) epidural or intrathecal, intraventricular (*see page 572*)
   B. different agents: local anesthetics, narcotics (without motor, sensory, or sympathetic impairment seen with local anesthetics) *see page 570*
3. intracranial ablative procedures:
   A. cingulotomy: theoretically reduces the unpleasant affect of pain without eliminating the pain. Must be done bilaterally, recently with MRI. Intolerable pain usually recurs after ≈ 3 mos. 10-30% develop flattened affect
   B. medial thalamotomy: controversial. May be useful for some for nociceptive cancer pain. Performed stereotactically, *see page 575*
   C. **stereotactic mesencephalotomy** 106: for unilateral head, neck, face and/or UE pain. Use MRI to create lesion 5 mm lateral to sylvian aqueduct at the level of the inferior colliculus. Unlike spinal cordotomy, the lesion is not near any motor tracts. Main complication is diplopia due to interference with vertical eye movement, often transient

4. spinal ablative surgical procedures
   A. cordotomy: *see below*
      1. open
      2. percutaneous
   B. cordectomy
   C. commissural myelotomy: for bilateral pain (*see page 570*)
   D. punctate midline myelotomy: for relief of visceral cancer pain
   E. dorsal root entry zone lesion: *see page 575*
   F. dorsal rhizotomy: not useful for large areas of involvement
   G. dorsal root ganglionectomy (an extraspinal procedure)
   H. sacral cordotomy: for patients with pelvic pain who have colostomy and ileostomy. A ligature is tied around the dural sac below S1 nerve roots
5. sympathectomy: possibly for causalgia major (see *Sympathectomy*, page 545 and *Complex regional pain syndrome (CRPS)* on page 576)
6. peripheral nerve procedures
   A. nerve block[107]:
      1. neurolytic: injection neurodestructive agents (e.g. phenol or absolute alcohol) on or near the target nerve
      2. nonneurolytic: using local anesthetics, sometimes in combination with corticosteroids
   B. neurectomy: (e.g. intercostal neurectomy for pain due to infiltration of chest wall by malignancy). Performed open or percutaneously with radiofrequency lesion. May sacrifice motor function with mixed nerves
   C. peripheral nerve stimulators: rarely discussed

20.4.1. Cordotomy

Interruption of the lateral spinothalamic tract fibers in the spinal cord. Cordotomy is the procedure of choice for unilateral pain below the C5 dermatomal level (≈ nipple)[A], in a terminally ill patient. Better for aching pain, poor for central pain, dysesthesias, causalgia (deafferentation pain) midline visceral pain. May be performed as an open procedure, but is more easily performed percutaneously at the C1-2 interspace (which limits the procedure to the cervical region). If there is any contralateral pain, it will tend to be magnified following the procedure and often leads to dissatisfaction with cordotomy. If

there is any bladder dysfunction, it will usually be worse following cordotomy. Bilateral cervical cordotomies carries a risk of the loss of automaticity of breathing[108] (one form of sleep apnea, so-called **Ondine's curse**[109]). Therefore, if bilateral cordotomies are desired, the second should be staged after normal respiratory function and CO_2 responsiveness are verified following the first procedure, or the second stage may be done as an open procedure in the thoracic region.

A. occasionally pain as high up as the mandible may be treated

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Review the cross sectional spinal cord anatomy for relationships of the critical tracts (spinothalamic and corticospinal) to the dentate ligament, the anterior spinal artery, respiratory (see *Figure 5-12*, page 93), and bladder areas (see *Figure 5-29*, page 117).

Pre-op evaluation

Spirometric measurement of minute volume before and after breathing a mixture of 5% CO_2 and 95% O_2 for 5 minutes. If the MV decreases, these patients are at increased risk of having sleep apnea (usually transient), no increased risk if MV increases or stays the same. Also, patients with < 50% of predicted values on PFTs are not candidates.

In patients with pulmonary cancer contralateral to the planned side of cordotomy, check that the contralateral diaphragm is functioning with fluoroscopy, otherwise if the ipsilateral diaphragm is lost due to cordotomy, the patient may be hypopneic.

Percutaneous cordotomy

Indicated for unilateral pain below ≈ C4-5 in a terminally ill patient. Radiofrequency current is used to lesion the lateral spinothalamic tract.

Technique

Patient does not need to be NPO. Usual pain medications should be given. The patient must be awake and cooperative (any movement with the needle in the cord may lacerate the cord), however one may give e.g. hydroxyzine (Vistaril®) 50 mg IM on call to procedure for relaxation.

The procedure is performed in the x-ray department with either fluoroscopic or CT guidance. For fluoroscopy, the head is placed in a Rosomoff headholder with the height adjusted to keep the mastoid process in the same horizontal plane as the acromioclavicular joint. Working on the side contralateral to the pain, local anesthetic without epinephrine is infiltrated 1 cm caudal to the mastoid tip. An 18 gauge lumbar puncture needle is inserted perfectly horizontal aiming halfway between the posterior margin of the body of C2 and the anterior portion of the C2 spinous process. Stay rostral to the C2 lamina to avoid the nerve (which is painful).

The dura will be penetrated at about the time that the tip of the needle is approximately even with the midline of the odontoid process on AP fluoro. A few ml of CSF are aspirated and shaken in a syringe together with a few ml of Pantopaque®[A], and several ml of the mixture are injected into the subarachnoid space under lateral fluoro guidance. Some dye will layer on the anterior cord, some on the dentate ligament, and most in the posterior thecal space. The dye will only stay momentarily on the dentate ligament, thus be ready to immediately advance the needle just barely anterior to this while monitoring the tip impedance which will jump from ≈ 300-500 Ω (ohms) in the CSF to ≈ 1200-1500 Ω as the spinal cord is penetrated.

A. Pantopaque is no longer available, and water soluble agents are less effective. A needle endoscopic technique may be able to localize the spinal cord anterior to the dentate ligaments

Stimulation at 100 Hz. should produce contralateral tingling at a threshold of ≤ 1 volt. No motor response should be elicited with 100 Hz. in the spinothalamic tract, and if muscle tetany occurs, lesioning must not be performed. If tingling is in the arm, lesioning will usually render from the arm and below analgesic. If tingling is in the lower extremity it will render only that limb analgesic. Stimulation at 2 Hz. should produce ipsilateral twitching of the arm or neck at ≈ 1-3 volts.

Radiofrequency lesioning is performed for 30 seconds while the patient sustains contraction of the ipsilateral hand and the voltage is gradually increased from zero. Any twitching of the hand is indication to back down on the voltage. A second lesion is performed in the same region and is usually less painful. The appropriate body area is then checked for analgesia to pinprick.

If the procedure is performed satisfactorily, an ipsilateral Horner's syndrome usually occurs.

Complications

For complications, *see* Table 20-6.

Outcome

In experienced hands, 94% will achieve at least significant pain relief at the time of hospital discharge. The level of analgesia falls with time. At 1 year 60% will be pain free, and at 2 years this will be only 40%. ab

Post-procedure management

CSF leakage will cease spontaneously. Patient is kept supine for 24 hrs to prevent "spinal" (post-LP) headache. Pain medication appropriate to post-operative management is prescribed. If successful, one can rapidly stop the narcotics for the primary pain, withdrawal syndromes occur only rarely.

Table 20-6 Post-cordotomy complications

Complication	Frequency
ataxia	20%
ipsilateral paresis	5% total 3% permanent
bladder dysfunction	10% total 2% permanent
postcordotomy dysesthesia	8%
sleep induced apnea	0.3% unilateral cordotomy 3% bilateral cordotomy
death (respiratory failure)	0.3% unilateral cordotomy 1.6% bilateral cordotomy

Open cervical cordotomy (Schwartz technique)

A relatively quick method for open cervical cordotomy[110]. Can theoretically be done under local for patients who cannot tolerate general anesthesia.

Technique

Position: prone; face carefully placed on padded horseshoe headrest, neck slightly flexed to open the interlaminar spaces and to lower the head to prevent accumulation of intracranial air.

Skin incision: midline from occiput to C3. Working only on the side contralateral to the pain, muscles are stripped off the posterior lip of the foramen magnum, and from the lamina of C1 and C2. A Schwartz or Gelpi retractor is

engaged between the occiput and C2. To increase exposure, the inferior half of C1 and superior half of C2 lamina are removed with a punch.

Dural incision: the ligamentum flavum is thin between C1-2, and can usually be opened with the dura in a linear incision from the lamina of C1 to C2 placed in the lateral third of the exposure, taking care to avoid bleeding from epidural veins. An angle is cut in the incision at either end to allow increased dural retraction. Tack-up sutures are placed in the dura, the arachnoid is opened, the dentate ligament is located and is gripped with a hemostat and divided between the hemostat and the dura.

Cordotomy: the dentate ligament is used to slightly rotate the spinal cord. A cordotomy knife (or 11 blade) with bone wax placed at 5 mm, is inserted into the cord in an avascular area just anterior to the dentate ligament, sharp side down. The anterolateral quadrant of the cord is cut with the following caveats:

- do not go posterior to the dentate ligament (to avoid corticospinal tract)
- do not cross the midline of the spinal cord
- do not injure the anterior spinal artery
- for patients with lower extremity pain, be sure to start exactly at the dentate ligament (to avoid missing lumbar and sacral fibers)

20.4.2. Commissural myelotomy

AKA mediolongitudinal myelotomy. Interrupts pain fibers crossing in the anterior commissure on their way to the lateral spinothalamic tract.

Indications: Bilateral or midline pain, primarily below the thoracic levels (including abdomen, pelvis, perineum and lower extremities).

Technique: Laminectomy must extend at least 3 levels above the highest dermatome involved in pain. The dura is opened longitudinally and the operating microscope is then used to identify the midline sulcus (this is usually very difficult to see, and is then estimated as being halfway between where the dorsal roots enter the cord). Veins in the mid-line are sacrificed for the length of the proposed incision. A number 11 scalpel blade is then placed in a hemostat with 6-7 mm of the tip exposed. The blade is inserted in the midline at the upper end of the desired incision and is then passed caudally for the length of the planned incision (usually 3-4 cm).

Outcome: 60% of patients have complete pain relief, 28% have partial, and 8% have none.

Complications: Weakness in the lower extremities occurs in ≈ 8% (usually lower motor neuron, presumably due to injury to anterior horn motor neurons). Dysesthesias occur in almost all patients, but persists > a few days in ≈ 16% (these patients also have impaired joint position sense, all of which are presumably due to posterior column injury). Bladder dysfunction is seen in ≈ 12%. Sexual dysfunction may also occur. There is a risk of injury to the anterior spinal artery (rare).

20.4.3. Punctate midline myelotomy

Indications: Pelvic and visceral pain refractory to other therapies[111].

Technique: Interruption of a midline posterior column pathway.

20.4.4. CNS narcotic administration

INTRASPINAL NARCOTICS

Spinal narcotics may be administered epidurally or intrathecally for pain relief. Satisfactory pain control can usually be achieved for pain below the neck, although for pain above the diaphragm/umbilicus some recommend intraventricular morphine[112] (*see page 572*). May also be performed on a "one-time" basis e.g. injection into epidural space following a lumbar laminectomy. Or, it may be given on a short term continuous basis, via an external epidural or intrathecal catheter. It may also be performed on an intermediateterm basis (< 60 days) with the use of a subcutaneous reservoir[113] or on a long-term basis with an implantable drug infusion pump[114] (e.g. Infusaid® or Medtronic® pump). Advantages over systemic narcotics include less sedation and/or confusion, less interference with GI motility (constipation), and possibly less N/V. The effectiveness is usually limited to ≈ 1 year and is thus not indicated for chronic benign pain. With time, increased doses are required because of the development of tolerance and/or progression of disease[115] with the concomitant development of the usual narcotic side effects.

SPINAL NARCOTICS

Must be preservative-free (for either intrathecal or epidural use). This may be prepared by a pharmacist (e.g. add enough preservative free 0.9% saline to 1 or 3

gm morphine sulfate powder to yield a total of 100 ml produces 10 or 30 mg/ml solution respectively, and then filter this through a 0.22 µm filter[116]). Alternatively, commercially available preparations include Duramorph® (available as 0.5 or 1 mg/ml) and Infumorph® (available in 20 ml ampules of 10 or 25 mg/ml), any of which may be diluted to a lower strength with preservative free diluent (normal saline). Cross tolerance to systemic narcotics does occur, and spinal narcotics are more effective in patients who have not been on continuous high dose IV opiates (patients on high-dose IV narcotics need higher initial intraspinal narcotic doses).

Side effects: include pruritus (often diffuse, and may be experienced most intensely in the nose), respiratory depression (the respiratory depression with spinal narcotics is usually very gradual, and is often easily detected by monitoring respiratory rate q 1 hr and taking action if the rate decreases), urinary retention, and N/V.

Trial injection

Before implanting a permanent delivery system a test injection should be performed to verify pain relief and tolerance for medication. Administered via percutaneously inserted epidural or intrathecal catheter connected to an external pump. Doses required for intrathecal catheters are usually ≈ 5-10 times lower than those for epidural catheters.

Sample post-injection orders after a one-time injection:

1. use no other narcotics for ≈ 24 hrs (with a continuous infusion additional narcotics should be withheld until the effect of the spinal narcotics has been determined)
2. 2 ampules (0.4 mg each) of naloxone (Narcan®) and syringe taped to patients bed (for the first 24 hrs after a single injection; at all times with continuous infusion)
3. head of bed elevated ≥ 10° for 24 hrs
4. record respiratory rate q[1] hr for 24 hrs; if asleep and respiratory rate < 10 breaths/min, awaken patient. If unable to awaken, administer naloxone 0.4 mg IV and notify physician. Repeat naloxone 0.4 mg IV q 2 min PRN

• optional: pulse oximeter for 24 hrs

5. diphenhydramine (Benadryl®) 25 mg IV q 1 hr PRN itching
6. droperidol (Inapsine®) 0.625 mg (which is 0.25 ml of the 2.5 mg/ml standard concentration available) IV q 30-60 mins PRN nausea
7. PRN supplemental pain medication:

A. narcotic agonist/antagonist: e.g. nalbuphine (Nubain®) 1-4 mg IV q 3 hrs

OR

B. ketorolac tromethamine (Toradol®) 15 mg IV or IM or 30 mg IM q 6 hrs (use lower dose for weight < 50 kg, age > 65 yrs, or reduced renal function)

IMPLANTABLE DRUG DELIVERY PUMPS

Although satisfactory pain control can be achieved with either epidural or intrathecal narcotics (morphine diffuses easily through the dura to the CSF where it gains access to pain receptors), epidural catheters commonly develop problems with scarring and may become less effective sooner than intrathecal catheters. Pumps should only be implanted if patients have successful pain control with test injection of spinal epidural (5-10 mg) or intrathecal (0.5-2 mg) morphine. A life expectancy of > 3 months is recommended for implantable pumps (if shorter longevity is anticipated, an external pump may be used).

One such series of commonly used implantable drug delivery pumps is manufactured by Infusaid [Infusaid, Inc., 1400 Providence Highway, Norwood, MA 02062, Phone: 1-800-451-1050]. The only needle that should be used with their devices are special 22 gauge Huber (non-coring) needles. Delivery rates increase with body temperature 10-13% per °C above 37° C, they decrease by the same amount for every °C below 37°C, and also they become inaccurate at ≤ 4 ml of reservoir fluid. These pumps should never be allowed to run until empty, as this may permanently affect accuracy and reliability of drug delivery. In addition to the pump reservoir port, most models have one or more side “bolus” ports that delivers injected fluid directly to the outlet tubing. One should not aspirate when accessing either port.

Medtronic produces a programmable pump.

Surgical insertion

Similar to the insertion of a lumbar-peritoneal shunt (*see page 213*). The patient is placed in the lateral position, such as on a bean-bag device. The pump is inserted into a subcutaneous pocket, created with a slightly curved 8-10 cm skin incision. The pump may be sutured to the fascia of the abdomen (in obese patients, it may be sutured to the subcutaneous tissue). Excess tubing should be coiled underneath the pump to prevent inadvertent puncture when accessing either reservoir.

The spinal catheter is inserted through a Tuohy needle inserted between

lumbar spinous processes either percutaneously or via a small incision 2-3 mm lateral to the spinous processes. Alternatively, it may be inserted directly via a hemilaminectomy. Fluoroscopy may be used intraoperatively to verify rostral placement of the catheter (radiographic visualization of the catheter may be aided by filling it with iodinated contrast, e.g Omnipaque-300, *see page 122*). All bends in the tubing should be very gradual to avoid kinking.

Post-op pain management:

Although the pump will be infusing when the patient leaves the operating room, unless they have been on intraspinal narcotics up until the time of surgery, it will usually take several days for the drug to reach equilibrium in the CSF before the level of pain control will be adequate. This can be mitigated by a bolus infusion (3-4 mg morphine for epidural catheters, or 0.2-0.4 mg for intrathecal catheters).

Complications

Meningitis and respiratory failure are rare complications. CSF fistula and spinal H/A may occur. Disconnection or dislodgment of catheter tip may result in failure to control pain, but can usually be surgically corrected.

Outcome

Cancer pain is significantly improved in up to 90%. Success rate for neuropathic pain (e.g. postherpetic neuralgia, painful diabetic sensory neuropathy): 25-50%.

INTRAVENTRICULAR NARCOTICS

Indications

May be used for cancer pain (especially head and neck)[117] unresponsive to other methods in patients with a life expectancy < 6 mos.

Technique

An intraventricular catheter is connected to a ventricular access device (*see page 211*). 0.5-1 mg of intrathecal morphine is injected via the VAD and usually provides ≈ 24 hrs of analgesia.

Complications

Side effects: common ones include dizziness, N/V. The risk of respiratory depression is minimized by using correct dosing. Complications in a series of 52 patients[117]: bacterial colonization of reservoir (4%), dislodged catheter (2%), blocked catheter (6%), postoperative meningitis (2%).

Outcome

Pain is successfully controlled in 70% at 2 mos, but thereafter the effectiveness diminishes as a result of tolerance to the narcotics.

20.4.5. Spinal cord stimulation (SCS)

Originally developed as **dorsal column stimulation (DCS)**, it has since been determined that pain relief also occurs with ventral stimulation (without stimulation induced paresthesias seen with DCS). Pain relief in humans persists beyond the stimulation time, and is not reversed by naloxone. The exact mechanism of action is un-determined, but probably involves some combination of neurohumoral (i.e. endorphin), antidromic stimulation of a spinal pain “gate”, and supraspinal center stimulation. GABA and serotonin levels have been shown to be increased with SCS.

Indications

1. pain[118]: postlaminectomy pain syndrome (the most common indication, especially if LE pain > back pain (*see below*)), complex regional pain syndrome (CRPS) (*see page 574*), postthoracotomy pain (intercostal neuralgia), multiple sclerosis, diabetic neuropathy (*see page 574*) and sometimes postherpetic neuralgia

✖ generally not used for cancer pain or for patients with limited life expectant

2. refractory angina pectoris: *see page 574*
3. painful limb ischemia from inoperable peripheral vascular disease: *see page 574*
4. functional: spastic hemiparesis, dystonia, bladder dysfunction

Technique

In order for SCS to be effective, it is necessary for the patient to feel the stimulation in the areas of pain[119]. Two techniques are used to place electrodes in the epidural space:

1. plate-like electrodes placed via hemilaminectomy
2. wire-like electrodes placed percutaneously with a Tuohy needle

Following electrode placement, a trial with an external generator over several days determines if SCS is effective. The electrodes are removed unless clear improvement occurs, in which case an implantable pulse generator is placed subcutaneously.

Complications

With plate electrodes, there is a 3.5% incidence of infection which respond to electrode removal and IV antibiotics. Less common complications: electrode migration (usually seen with first few weeks), lead breakage (less common with present systems), CSF leak, radicular pain, intermittent interference with cardiac pacemakers, and weakness.

Outcome

Success rate in pain control is ≈ 50% improvement in 50% of patients in experienced hands at specialized centers where multidisciplinary approach is available[119]. In a retrospective long-term follow-up study (ave = 96 months) of 410 patients that had SCS implantation due to numerous indications, success rate was 74%[120].

Prognosticators of a poor response to SCS include: pain resulting from spinal cord injury, from lesions proximal to the ganglion (e.g. root avulsion), failed back syndrome with back pain > LE pain and multiple previous operations (*see below*), psychological factors such as litigation, workers compensation, familial/marital discord or drug seeking behavior[121].

SPECIFIC SYNDROMES TREATED

Failed back surgery syndrome

Σ The addition of SCS improves pain control over either PT or medical management alone for failed back surgery syndrome. At 24 months, SCS is as effective as reoperation in treating radicular pain, with no difference in ADLs or work status.

In the PROCESS trial[122] (Prospective Randomized Controlled Multicenter Trial of the Effectiveness of Spinal Cord Stimulation), 100 patients with failed back surgery syndrome were randomized to SCS placement plus conventional medical management (52 patients) vs. conventional medical management alone (48 patients). The health-related quality of life, measured using EuroQol-5D questionnaire, was greater in the SCS group despite a higher total health care cost at 6 months.

In long-term follow-up at 24 months, the primary outcome (>50% relief in leg pain) is achieved in 37% of patients that were randomized to SCS plus conventional medical management and 2% of patients that were randomized to conventional medical management only. Patients were allowed to cross-over. After cross-over, the primary outcome is achieved in 47% of patients (34 of 72) who had SCS plus medical management as final treatment versus 7% of patients (1 of 15) in the other group (P=0.02)[123].

In another randomized prospective study, patients with persistent or recurrent radicular pain after lumbosacral surgery were randomized to reoperation vs. SCS. On an average of 3-year follow-up, the SCS group required less opiate analgesics. 9 of 19 patients in the SCS group compared to only 3 of 26 patients reoperated had self reported pain relief and satisfaction (P < 0.01), and there was no difference in ADLs and work status. Patients in the SCS group were less likely to crossover to undergo reoperation (5 of 24 patients from the SCS group versus 14 of 26 patients in the reoperation group, P = 0.02)[124].

Complex regional pain syndrome

Σ SCS may be effective for treating CRPS during the first couple of years, however no significant benefit was evident at 5-year follow-up.

CRPS is a chronic pain condition marked by continuous disabling intense aching or burning pain. Type I has no known nerve injury, Type II follows a nerve injury (*see page 576*). In a randomized clinical trial[125], patients with CRPS Type I were randomized to receive SCS plus physical therapy **(PT)** (36 patients) or PT alone (18 patients). 24 of 36 patients had successful SCS trial and underwent implantation. At 6 months, in the group that received SCS plus PT, pain intensity reduced by 2.4 cm on the visual-analogue scale as opposed to an increase of 0.2 cm in the PT only group (P<0.001). In addition, 39% of patients in the SCS group, had "much improved" globally perceived effect vs. 6% (P=0.01). The health-related quality of life only improved in the SCS group. At

2-year follow-up, pain intensity in the SCS group reduced by 2.1 vs. 0.0 cm in the PT group compared to baseline ($P < 0.001$) and global perceived effect were "much improved" in 43% vs. 6% ($P = 0.001$)[126]. However, these benefits were no longer significant in 5 years[127].

Peripheral vascular disease

> Σ SCS does help with pain due to inoperable limb ischemia. It may or may not improve healing of pressure ulcers

In a retrospective, non-control study of 38 patients, ≈ 94% experienced pain relief and ≈ 50% experienced healing of ischemic ulcers[128].

In a recent review[129] of six controlled studies of nearly 450 patients, SCS + medical treatment was compared to medical treatment alone. Although there was no significant difference in ulcer healing, the use of analgesics was less and limb salvage after 12 months was significantly higher in the SCS group (relative risk = 0.71).

Angina pectoris

> Σ SCS was as effective as CABG in controlling refractory angina and protecting against MIs. SCS improves exercise capacity by an unknown mechanism

SCS reduces anginal pain and improves exercise capacity by an unknown mechanism, which may be related to decrease in myocardial oxygen consumption[130] or altering myocardial blood flow[131] rather than just masking symptoms

In a multicenter, randomized, prospective clinical trial, comparing SCS to CABG in selected patient[132], there was no significant difference in decreasing anginal attack and nitrates consumption between the groups. 5-year follow-up from this trial found that both CABG and SCS offered similar protection from angina pectoris and myocardial infarction[133].

In a prospective study of 104 patients who underwent SCS placement for refractory angina pectoris (average follow-up ≈ 13 months), 73% had > 50% reduction of weekly anginal episodes compared to baseline[134].

Diabetic Neuropathy

> Σ Available data is limited, but SCS may be a viable modality for refractory pain from diabetic neuropathy. Further study is needed

No good clinical data are available. A few studies with small numbers of patients suggest SCS can provide significant pain relieve in most patients with diabetic neuropathy that failed conservative management[135-137].

A small prospective, open-label study reported 9 of 11 patients with diabetic neuropathy that failed conservative treatment had significant pain relieved after SCS implantation at 6 months. Pain score on visual analogue scale decreased from 77 to 34. Microcirculatory perfusion did not change significantly from baseline[137].

20.4.6. Deep brain stimulation (DBS)

Deafferentation pain syndromes (anesthesia dolorosa, pain from spinal cord injury, or thalamic pain syndromes) may benefit from stimulation of sensory thalamus (ventral posteromedial **(VPM)** or ventral posterolateral **(VPL)**). DBS for chronic neuropathic pain produces a 40-50% reduction in pain in about 25-60% of patients[138].

Nociceptive pain syndromes are more likely to benefit from stimulation of periventricular gray matter **(PVG)** or periaqueductal gray matter **(PAG)** although PAG stimulation is rarely used because it often produces unpleasant side effects. Still, response rate has been only ≈ 20%[139] resulting in failure of the FDA to approve these devices for pain.

Cluster headaches: may respond to hypothalamic stimulation, but larger trials with longer follow-up are needed[138].

20.4.7. Dorsal root entry zone (DREZ) lesions

Although use has been reported for a variety of indications, DREZ lesions appear to be most effective in treating the following:

1. deafferentation pain resulting from nerve root avulsion[140-142]. This most commonly occurs in motorcycle accidents
2. spinal cord injuries **(SCI)** with pain around the lowest spared dermatome with caudal extension of pain restricted to a few dermatomes (SCI with

diffuse pain involving the entire body and limbs below the injury is less responsive)

3. post herpetic neuralgia (*see page 564*): usually good initial response, but early recurrence in ≤ few months is common, and only 25% have long-term relief of pain
4. postamputation phantom limb pain: there is some support for this in the literature, but others feel this is not a good indication[68]
5. ✖ generally not used for cancer pain

Technique: A laminectomy is performed over the involved segment(s) using radiographic localization. The dura is opened, and the DREZ is identified under microscope magnification using intact posterior rootlets above or below for orientation (contralateral rootlets may also be used to estimate the mirror-image location). Lesions are created ipsilateral to the avulsed nerve roots by radiofrequency current (approximately 50-60 lesions are required for several segments, each lesion is done at 75° for ≈ 15 seconds) or selective incisions extending from the last completely normal rootlet at the rostral end to the first normal rootlet caudally. The lesioning needle or knife blade is angled 30-45° medially and inserted to a depth of 2-3 mm. DREZ lesions may be combined with a cordectomy at the level of anatomic cord disruption in paraplegic patients[68].

Post-op management: Bed rest for 3 days may reduce the risk of CSF leakage. Analgesics appropriate for a multilevel laminectomy are administered.

Complications: Ipsilateral weakness (related to corticospinal tract) or loss of proprioception (dorsal columns) occurs in 10% of patients, and is permanent in ≈ half (i.e. 5%).

Outcome: In pain related to brachial plexus avulsion, 80-90% long-term significant improvement can be expected. Paraplegics with pain limited to the region of injury have an 80% rate of improvement, compared to 30% for those with pain involving the entire body below the lesion.

20.4.8. Thalamotomy

Controversial & rarely used. Not a routine treatment for pain. May be useful for some nociceptive cancer pain, especially of head, neck and face. Neuropathic pain syndromes respond infrequently. The target is the medial thalamus which

exhibits high-frequency bursts associated with deafferentation pain.

Pre-op preparation: CT and/or MRI is used to rule-out mass lesion and to establish target coordinates. Platelet count and coagulation studies must be within normal limits. NSAIDs should be discontinued 10 d pre-op. HTN must be avoided during surgery.

Technique

A stereotactic frame is applied parallel to the orbitomeatal line. MRI shows the anterior **(AC)** and posterior commissure **(PC)** to better advantage than CT, but suffers from some geometric inaccuracies (shift and distortion). A burr hole is placed 2 cm lateral to the midline just anterior to the coronal suture. A radiofrequency probe is inserted to the medial thalamus and then electrophysiologic localization of the target is performed. Following the procedure, a CT scan is done to rule-out hemorrhage.

Complications

Mortality: < 1%. Morbidities: significant hemorrhage: 0.5%, subdural hematoma: 0.5%, hemiparesis: 1%, cognitive impairment: 20-70%. Aphasia occurs infrequently.

Outcome

Significant pain control occurs in ≈ 50% of those with cancer pain, but recurrence of pain is common and is seen in 60% at 6 months. Only ≈ 20% of cases of neuropathic pain respond.

20.5. Complex regional pain syndrome (CRPS)

The terminology is confusing. Formerly also called causalgia (reflex sympathetic dystrophy). The term causalgia (Greek: *kausis* - burning, *algos* - pain) was introduced by Weir Mitchell in 1864. It was used to describe a rare syndrome that followed a minority of partial peripheral nerve injuries in the American civil war. Triad: burning pain, autonomic dysfunction and trophic changes.

CRPS Type II (AKA **major causalgia**) follows nerve injury (originally described after high velocity missile injuries). CRPS Type I (AKA reflex sympathetic dystrophy or **causalgia minor**) denoted less severe forms, and has

been described after non-penetrating trauma[143]. Shoulder-hand syndrome and Sudek's atrophy are other variant designations. In 1916, the autonomic nervous system was implicated by René Leriche, and the term **reflex sympathetic dystrophy (RSD)** later came into use[144] (but RSD may be distinct from causalgia[145]).

Post-op CRPS has been described following carpal tunnel surgery as well as surgery on the lumbar[146] (*see page 450*) and cervical spine.

At best, CRPS must be regarded as a *symptom complex*, and not as a discrete syndrome nor medical entity (see the essay by Ochoa[147]). Patients exhibiting CRPS phenomenology are not a homogeneous group, and include[148]:

1. actual CRPS (for these, Mailis proposes the term "physiogenic RSD"): a complex set of neuropathic phenomena that may occur with *or* without nerve injury
2. medical conditions distinct from CRPS but with signs and symptoms that mimic CRPS: vascular, inflammatory, neurologic…
3. the product of mere immobilization: as in severe pain avoidance behavior, or at times psychiatric disorders
4. part of a factitious disorder with either a psychological basis (e.g. Munchausen's syndrome) or for secondary gain (financial, drug seeking…) i.e. malingering

Pathogenesis

Early theories invoked ephaptic transmission between sympathetics and afferent pain fibers. This theory is rarely cited currently. Another more recent postulate involves nor-epinephrine released at sympathetic terminals together with hypersensitivity secondary to denervation or sprouting. Many modern hypotheses do not even embrace involvement of the autonomic nervous system in all cases[144, 145, 148].

Thus, many of the alterations seen in CRPS may simply be epiphenomena rather than part of the etiopathogenetic mechanism.

Clinical

CRPS may be described as a phenomenology, i.e. a variable complex of signs and symptoms due to multiple etiologies included in this nonhomogeneous group[148]. No diagnostic criteria for the condition have been established, and various investigators select different factors to include or exclude patients from

their studies.

Symptoms

Pain: affecting a limb, usually burning, and prominent in the hand or foot. Onset in the majority is within 24 hrs of injury (unless injury causes anesthesia, then hrs or days may intervene); however, CRPS may take days to weeks to develop. Median, ulnar and sciatic nerves are the most commonly cited involved nerves. However, it is not always possible to identify a specific nerve that has been injured. Almost any sensory stimulus worsens the pain (**allodynia** is pain induced by a nonnoxious stimulus).

Signs

The physical exam is often difficult due to pain.

Vascular changes: either vasodilator (warm and pink) or vasoconstrictor (cold, mottled blue). Trophic changes (may be partly or wholly due to immobility): dry/scaly skin, stiff joints, tapering fingers, ridged uncut nails, either long/course hair or loss of hair, sweating alterations (varies from anhidrosis to hyperhidrosis).

Diagnostic aids

In the absence of an agreed upon etiology or pathophysiology, there can be no basis for specific tests, and the lack of a "gold-standard" diagnostic criteria makes it impossible to verify the authenticity of any diagnostic marker. Numerous tests have been presented as aids to the diagnosis of CRPS, and essentially all have eventually been refuted. Candidates have included:

1. thermography: discredited in clinical practice
2. three-phase bone scan: typical CRPS changes also occur after sympathectomy[149], which has traditionally been considered curative of CRPS
3. osteoporosis on x-ray[150], particularly periarticular demineralization: nonspecific
4. response to sympathetic block (once thought to be the sine qua non for causalgia major and minor, the response sought was relief (complete or significant) with sympathetic block of appropriate trunk (stellate for UE, lumbar for LE)): has failed to hold up once stringent placebo-controlled trials were executed

5. various autonomic tests[151]: resting sweat output, resting skin temperature, quantitative sudomotor axon reflex test

Treatment

In the absence of a delineated pathophysiology, treatment is judged purely by subjective impression of improvement. CRPS treatment studies have had an unusually high placebo response rate[152]. Medical therapy is usually ineffective. Proposed treatments include:

1. tricyclic antidepressants
2. 18-25% have satisfactory long-lasting relief after a series of sympathetic blocks (see *Stellate ganglion block* and *Lumbar sympathetic block* starting on *page 215*), although one report found no long-lasting benefit in any of 30 patients[153]
3. intravenous regional sympathetic block, particularly for UE CRPS: agents used include guanethedine154 20 mg, reserpine, bretylium…, injected IV with arterial tourniquet (sphygmomanometer cuff) inflated for 10 min. If no relief, repeat in 3-4 wks. No better than placebo in several trials[155, 156]
4. surgical sympathectomy (*see page 545*): some purport that this relieves pain in > 90% of patients (with a few retaining some tenderness or hyperpathia). Others opine that there is no rational reason to consider sympathectomy since sympathetic blocks have been shown to be no more effective than placebo[144]
5. spinal cord stimulation: some success has been reported

20.6. References

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NOTES

21. Tumor

21.1. General information

CLASSIFICATION OF NERVOUS SYSTEM TUMORS

WHO classification of tumors of the nervous system[1-5]

The 2007 WHO classification[5] identifies 7 categories of tumors of the nervous system (*see Table 21-1*) and a modified outline appears below (along with the unofficial category "intracranial and/or intraspinal embryonal remnants", and pituitary adenomas (not part of the CNS)). Also to be considered: cysts (neurocysticercosis…), tumor-like masses (e.g. giant aneurysms), and local extension of regional tumors. Cytogenetic and molecular genetic information are playing an ever increasing role in the definitive classification of some tumors.

Table 21-1 Overview of WHO classification of nervous system tumors[2]

1. tumors of neuroepithelial tissue
2. tumors of cranial and paraspinal nerves
3. tumors of the meninges
4. lymphomas and hematopoietic neoplasms
5. germ cell tumors
6. tumors of the sellar region
7. metastatic tumors

	ICD-O*	Page
A. TUMORS OF NEUROEPITHELIAL TISSUE†		
1. astrocytes ß astrocytic tumors‡		518
A. astrocytomas that are typically infiltrating (lower grade tumors in this category tend to progress in malignancy)		518
1. diffuse astrocytoma (WHO II§). Variants:	9400/3	518

a. fibrillary	9420/3	
b. protoplasmic	9410/3	
c. gemistocytic	9411/3	
2. anaplastic (malignant) astrocytoma (WHO III)	9401/3	595
3. glioblastoma (WHO IV) (formerly glioblastoma multiforme **(GBM))**. Variants:	9440/3	596
a. giant cell glioblastoma	9441/3	
b. gliosarcoma	9442/3	
4. gliomatosis cerebri	9381/3	598
B. more circumscribed lesions (these do <u>not</u> tend to progress to anaplastic astrocytoma and GBM)		
1. pilocytic astrocytoma	9421/1	603
• pilomyxoid astrocytoma (WHO II)	9425/3	606
2. pleomorphic xanthoastrocytoma **(PXA)**	9424/3	592
3. subependymal giant cell astrocytoma: associated with tuberous sclerosis	9384/1	725
2. oligodendrocytes → oligodendroglial tumors		
A. oligodendroglioma (WHO II)	9450/3	609
B. anaplastic oligodendroglioma (WHO III)	9451/3	610
3. oligoastrocytic tumors (nee: mixed gliomas)		
A. oligoastrocytoma (WHO II)	9382/3	612
B. anaplastic (malignant) oligoastrocytoma (WHO III)	9382/3	612
4. ependymocytes → ependymal tumors		
A. ependymoma (WHO II). Variants:	9391/3	682
1. cellular	9391/3	683
2. papillary	9393/3	683
3. clear cell	9391/3	683
4. tanycytic	9391/3	683
B. anaplastic (malignant) ependymoma (WHO III)	9392/3	683
C. myxopapillary ependymoma: filum terminale only (WHO I)	9394/1	683
D. subependymoma (WHO I)	9383/1	683
5. choroid plexus tumors		
A. choroid plexus papilloma	9390/0	695
B. atypical choroid plexus papilloma	9390/1	695
C. choroid plexus carcinoma	9390/3	695
6. other neuroepithelial tumors		696

A. astroblastoma	9430/3	
B. chordoid glioma of the 3rd ventricle	9444/1	696
C. angiocentric glioma	9431/1	
7. neuronal and mixed neuronal-glial tumors		612
A. gangliocytoma	9492/0	
B. ganglioglioma	9505/1	677
C. dysembryoplastic neuroepithelial tumor **(DNT)**	9413/0	591
D. desmoplastic infantile astrocytoma/ganglioglioma **(DIG)**	9412/1	612
E. dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	9493/0	593
F. anaplastic (malignant) ganglioglioma	9505/3	
G. central neurocytoma	9506/1	612
H. extraventricular neurocytoma	9506/1	
I. cerebellar liponeurocytoma	9506/1	
J. papillary glioneuronal tumor	9509/1	
K. rosette-forming glioneuronal tumor of the 4th ventricle	9509/1	
L. paraganglioma (of the filum terminale	8680/1	
8. pinealocytes → pineal parenchymal tumors		
A. pineocytoma (pinealoma)	9361/1	692
B. pineoblastoma	9362/3	692
C. pineal parenchymal tumor of intermediate differentiation	9362/3	
D. papillary tumor of the pineal region	9395/3	
9. embryonal tumors		685
A. medulloblastoma. Variants:	9470/3	686
1. desmoplastic/nodular medulloblastoma	9471/3	687
2. anaplastic medulloblastoma	9474/3	
3. large-cell medulloblastoma	9474/3	687
4. medulloblastoma with extensive nodularity	9471/3	
B. CNS primitive neuroectodermal tumors **(PNET)**	9473/3	686
1. CNS neuroblastoma	9500/3	
2. CNS ganglioneuroblastoma	9490/3	
3. medulloepithelioma	9501/3	
4. ependymoblastoma	9392/3	688
C. atypical teratoid/rhabdoid tumor **(AT/RT)**	9508/3	688

B. TUMORS OF CRANIAL, SPINAL AND PERIPHERAL NERVES		
1. schwannoma (neurilemmoma, neurinoma) (vestibular schwannoma AKA acoustic neuroma, 620)	9560/0	
A. cellular	9560/0	
B. plexiform	9560/0	
C. melanotic	9560/0	
2. neurofibroma	9540/0	722
A. plexiform	9550/0	723
3. perineurioma	9571/0	696
A. perineurioma, NOS	9571/0	696
B. malignant perineurioma	9571/3	697
4. malignant peripheral nerve sheath tumor **(MPNST)** (neurogenic sarcoma, anaplastic neurofibroma, "malignant schwannoma"). Variants:	9540/3	
A. epithelioid MPNST	9540/3	
B. MPNST with mesenchymal differentiation	9540/3	
C. melanotic MPNST	9540/3	
D. MPNST with glandular differentiation	9540/3	
C. TUMORS OF THE MENINGES		
1. tumors of meningothelial cells		
A. meningioma. Variants:	9530/0	613
1. meningothelial (WHO I)	9531/0	
2. fibrous (fibroblastic) (WHO I)	9532/0	
3. transitional (mixed) (WHO I)	9537/0	
4. psammomatous (WHO I)	9533/0	
5. angiomatous (WHO I)	9534/0	
6. microcystic (WHO I)	9530/0	
7. secretory (WHO I)	9530/0	
8. lymphoplasmacyte-rich (WHO I)	9530/0	
9. metaplastic (WHO I)	9530/0	
• the following meningiomas exhibit more malignant behavior		
10. clear cell (intracranial) (WHO II)	9538/1	
11. chordoid (WHO II)	9538/1	
12. atypical meningioma (WHO II)	9539/1	616
13. papillary meningioma (WHO III)	9538/3	

14. rhabdoid meningioma (WHO III)	9538/3	615
15. anaplastic (malignant) meningioma (WHO III)	9530/3	616
2. mesenchymal, non-meningothelial tumors		620
A. lipoma (e.g. of corpus callosum, *page 246*)	8850/0	
B. angiolipoma	8861/0	
C. hiberneuroma	8880/0	
D. liposarcoma (intracranial)	8850/3	
E. solitary fibrous tumor	8815/0	
F. fibrosarcoma	8810/3	
G. malignant fibrous histiocytoma	8830/3	
H. leiomyoma	8890/0	
I. leiomyosarcoma	8890/3	
J. rhabdomyoma	8900/0	
K. rhabdomyosarcoma	8900/3	
L. chondroma	9220/0	
M. chondrosarcoma	9220/3	
N. osteoma	9180/0	
O. osteosarcoma	9180/3	
P. osteochondroma	9210/0	
Q. hemangioma	9120/0	
R. epithelioid hemangioendothelioma	9133/1	
S. hemangiopericytoma	9150/1	620
T. anaplastic hemangiopericytoma	9150/3	
U. angiosarcoma	9120/3	
V. Kaposi sarcoma	9140/3	
W. Ewing sarcoma - PNET	9364/3	
3. primary melanocytic lesions		
A. diffuse melanocytosis	8728/0	
B. melanocytoma	8728/1	
C. malignant melanoma (primary CNS)	8720/3	697
D. meningeal melanomatosis	8728/3	
4. other neoplasms related to the meninges		
A. hemangioblastoma	9161/1	667

D. LYMPHOMAS AND HEMATOPOIETIC NEOPLASMS		
1. malignant lymphoma (primary CNS lymphoma)	9590/3	672
2. plasmacytoma	9731/3	
3. granulocytic sarcoma	9930/3	
E. GERM CELL TUMORS		
1. germinoma	9064/3	692
2. embryonal carcinoma	9070/3	
3. endodermal sinus tumor **(EST)** (yolk sac tumor)	9071/3	
4. choriocarcinoma	9100/3	
5. teratoma (from all 3 germ-cell layers)	9080/1	692
A. mature	9080/0	
B. immature	9080/3	
C. teratoma with malignant transformation	9084/3	
6. mixed germ cell tumors	9085/3	
F. TUMORS OF THE SELLAR REGION		
1. craniopharyngioma. Variants:	9350/1	663
A. adamantinomatous	9351/1	
B. papillary	9352/1	
2. adenohypophyseal cells → pituitary adenomaΔ	8272/0	633
A. prolactinomaΔ	8271/0	637
B. ACTH secreting adenoma		638
C. growth-hormone secreting adenoma		639
D. thyrotropin (TSH) secreting adenoma		640
E. gonadotropin (LH and/or FSH) secreting adenoma		
3. neurohypophysis and infundibulum		
A. granular cell tumor	9582/0	641
B. neurohypophyseal cells	9432/1	641
4. pituitary carcinoma		634
5. spindle cell oncocytoma of the adenohypophysis	8291/0	
G. METASTATIC TUMORS: those commonly involving brain include:		702
1. lung cancer: especially small-cell (*see page 703*)		703
2. breast		
3. melanoma		704
4. renal cell		

		705
5. lymphoma		
6. GI		
H. LOCAL EXTENSIONS FROM REGIONAL TUMORSΔ		
1. paraganglioma (chemodectoma)		
A. glomus jugulare tumor		680
2. notochord → chordoma		675
3. carcinoma		
I. CYSTS AND TUMOR-LIKE LESIONSΔ		
1. Rathke's cleft cyst		665
2. ectodermal rests		
A. epidermoid cyst		689
B. cholesteatoma		689
3. dermoid cyst		688
4. colloid cyst of the third ventricle		665
5. neurenteric/enterogenous cyst		227
6. neuroglial cyst		
7. hypothalamic neuronal hamartoma		226
8. nasal glial heterotopia		
9. plasma cell granuloma		
J. UNCLASSIFIED TUMORSΔ		

* ICD-O = morphology code of the International Classification of Diseases for Oncology (http://www.iarc.fr/WHO-BlueBooks/). The extension after the slash is the "behavior code": /0 = benign, /1 = low or uncertain malignant potential or borderline malignancy, /2 = in situ lesions, /3 = malignant tumors

† represents a significant portion of what is usually considered to be primary brain tumors

‡ the term "**glioma**" is occasionally used to refer to all glial tumors (e.g. "low-grade glioma" is often used when discussing low-grade tumors of any glial lineage, see page 590), although in its usual sense glioma (especially "high grade gliomas") refers only to astrocytic tumors

§ "WHO II" means World Health Organization (WHO) grade II, "WHO III" means WHO grade III, etc.

Δ these tumors are not part of the 2007 WHO classification[5]

21.1.1. Brain tumors - general clinical aspects

Presentation

The most common presentation of brain tumors is progressive neurologic

deficit (68%), usually motor weakness (45%). Headache was a presenting symptom in 54% (*see below*), and seizures in 26%. For details of presentation, see sections below for supratentorial and infratentorial tumors.

SUPRATENTORIAL TUMORS[6]

Signs and symptoms include:

1. those due to increased ICP (see *Infratentorial tumors* below):
   A. from mass effect of tumor and/or edema
   B. from blockage of CSF drainage (hydrocephalus): less common in supratentorial tumors (may occur e.g. with colloid cyst, entrapped lateral ventricle)
2. progressive focal deficits: includes weakness, dysphasia (which occurs in 37-58% of patients with left-sided brain tumors[7]): *see below*
   A. due to destruction of brain parenchyma by tumor invasion
   B. due to compression of brain parenchyma by mass and/or peritumoral edema and/or hemorrhage
   C. due to compression of cranial nerve(s)
3. headache: *see below*
4. seizures: not infrequently the first symptom of a brain tumor. Tumor should be aggressively sought in an idiopathic first time seizure in a patient > 20 years (if negative, the patient should be followed with repeat studies at later dates). Rare with posterior fossa tumors or pituitary tumors
5. mental status changes: depression, lethargy, apathy, confusion
6. symptoms suggestive of a TIA (dubbed "tumor TIA") or stroke, may be due to:
   A. occlusion of a vessel by tumor cells
   B. hemorrhage into the tumor: any tumor may hemorrhage, see *Hemorrhagic brain tumors*, page 1123
   C. focal seizure
7. in the special case of pituitary tumors (see *Pituitary tumors*, page 633):
   A. symptoms due to endocrine disturbances
   B. pituitary apoplexy: *see page 635*
   C. CSF leak

Booking the case - craniotomy for supratentorial

tumor

Also see defaults & disclaimers (*page v*). If awake craniotomy is required, then *see page 151*.

1. position: (depends on location of tumor)
2. pre-op embolization (by neuroendovascular interventionalist) for some vascular tumors including some meningiomas
3. equipment:
   A. microscope
   B. ultrasonic aspirator
   C. image guidance system
4. blood availability: type and cross 2 U PRBC
5. post op: ICU
6. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the skull remove as much of the tumor as is safely possible
   B. alternatives: nonsurgical management, radiation therapy for some tumors
   C. complications: (usual craniotomy complications - *see page v*) *plus* inability to remove all of the tumor

INFRATENTORIAL TUMORS

Seizures are rare (unlike supratentorial tumors, (seizures arise from irritation of cerebral cortex).

1. most posterior fossa tumors present with signs and symptoms of increased intracranial pressure **(ICP)** due to hydrocephalus **(HCP)**. These include:
   A. headache: (*see below*)
   B. nausea/vomiting: due either to increased ICP from HCP, or from direct pressure on the vagal nucleus or the area postrema (“vomiting center”)
   C. papilledema: estimated incidence is ≈ 50-90% (more common when the tumor impairs CSF circulation)
   D. gait disturbance/ataxia
   E. vertigo
   F. diplopia: may be due to VI nerve (abducens) palsy which may occur with increased ICP in the absence of direct compression of the nerve (*see page 836*)

2. S/S indicative of mass effect in various locations within the p-fossa
   A. lesions in cerebellar hemisphere may cause: ataxia of the extremities, dysmetria, intention tremor
   B. lesions of cerebellar vermis may cause: broad based gait, truncal ataxia, titubition
   C. brainstem involvement usually results in multiple cranial nerve and long tract abnormalities, and should be suspected when nystagmus is present (especially rotatory or vertical)

Booking the case - craniotomy for infratentorial tumor

Also see defaults & disclaimers (*page v*). For retromastoid surgery for vestibular schwannomas, *see page 629*.

1. position: (typically either prone or park bench, depending on tumor type/location and surgeon preference)
2. pre-op embolization (by neuroendovascular interventionalist) for some vascular tumors such as hemangioblastoma
3. equipment:
   A. microscope
   B. ultrasonic aspirator
   C. image guidance system (optional)
4. blood availability: type and cross 2 U PRBC
5. post op: ICU
6. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the skull remove as much of the tumor as is safely possible
   B. alternatives: nonsurgical management, radiation therapy for some tumors
   C. complications: (usual craniotomy complications - *see page v*) *plus* inability to remove all of the tumor, hydrocephalus, CSF leak

FOCAL NEUROLOGIC DEFICITS ASSOCIATED WITH BRAIN TUMORS

In addition to nonfocal signs and symptoms (e.g. seizures, increased ICP…),

as with any destructive brain lesion tumors may produce progressive deficits related to the function of the involved brain. Some characteristic “syndromes”:

1. frontal lobe: abulia, dementia, personality changes. Often nonlateralizing, but apraxia, hemiparesis or dysphasia (with dominant hemisphere involvement) may occur
2. temporal lobe: auditory or olfactory hallucinations, déja vu, memory impairment. Contralateral superior quadrantanopsia may be detected on visual field testing
3. parietal lobe: contralateral motor or sensory impairment, homonymous hemianopsia. Agnosias (with dominant hemisphere involvement) and apraxias may occur (see *Clinical syndromes of parietal lobe disease*, page 113)
4. occipital lobe: contralateral visual field deficits, alexia (especially with corpus callosum involvement with infiltrating tumors)
5. posterior fossa: (*see above*) cranial nerve deficits, ataxia (truncal or appendicular)

HEADACHES WITH BRAIN TUMORS

Headache **(H/A)** may occur with or without elevated ICP. Present equally in patients with primary or metastatic tumor (≈ 50% of patients[8]). Classically described as being worse in the morning (possibly due to hypoventilation during sleep), this may actually be uncommon[8]. Often exacerbated by coughing, straining, or (in 30%) bending forward (placing head in dependent position). Associated with nausea and vomiting in 40%, may be temporarily relieved by vomiting (possibly due to hyperventilation during vomiting). These features along with the presence of a focal neurologic deficit or seizure were thought to differentiate tumor H/A from others. However, H/A in 77% of brain tumor patients were similar to tension H/A, and in 9% were migraine-like[8]. Only 8% showed the “classic” brain tumor H/A, two thirds of these patients had increased ICP.

Etiologies of tumor headache: The brain itself is not pain sensitive. H/A in the presence of brain tumor may be due to any combination of the following:

1. increased intracranial pressure **(ICP)**: which may be due to
   A. tumor mass effect
   B. hydrocephalus (obstructive or communicating)
   C. mass effect from associated edema
   D. mass effect from associated hemorrhage

2. invasion or compression of pain sensitive structures:
   A. dura
   B. blood vessels
   C. periosteum
3. secondary to difficulty with vision
   A. diplopia due to dysfunction of nerves controlling extra-ocular muscles
      1. direct compression of III, IV, or VI
      2. abducens palsy from increased ICP (*see* diplopia *on page 586*)
      3. internuclear ophthalmoplegia due to brainstem invasion/compression
   B. difficulty focusing: due to optic nerve dysfunction from invasion/compression
4. extreme hypertension resulting from increased ICP (part of Cushing's triad)
5. psychogenic: due to stress from loss of functional capacity (e.g. deteriorating job performance)

FAMILIAL SYNDROMES

Several familial syndromes are associated with CNS tumors as shown in *Table 21-2* (with page number locations).

Turcot syndrome[10]: a rare inherited disorder characterized by multiple colorectal neoplasms (carcinomas or benign adenomatous polyps) together with neuroepithelial tumors of the CNS (GBM, AA, MB, pineoblastoma, ganglioglioma & ependymoma). **Type 1**: GBM without familial polyposis (but often with nonpolyposis colorectal cancer). Mean survival of Turcot patients with GBM is 27 months (longer than sporadic cases). **Type 2**: MB & familial adenomatous polyposis.

Li-Fraumeni syndrome: rare (< 400 families identified) inherited autosomal dominant mutation of the TP53 tumor suppressor gene. Patients have increased incidence of multiple types of tumors, including: sarcoma & osteosarcoma, breast cancer, astrocytoma and PNET, adrenocortical carcinoma, leukemia.

Table 21-2 Familial syndromes associated with CNS tumors

Syndrome	Page	CNS tumor
von Hippel-Lindau	667	hemangioblastoma

tuberous sclerosis	725	subependymal giant cell astrocytoma
neurofibromatosis type I	723	optic glioma, astrocytoma, neurofibroma
neurofibromatosis type II	724	vestibular schwannoma, meningioma, ependymoma, astrocytoma
Turcot syndrome (BTP syndrome)[9]	588	GBM, AA, & medulloblastoma, pineoblastoma
Li-Fraumeni	588	astrocytoma, PNET
Cowden	593	meningiomas
Lhermitte-Duclos	593	

STEROID USE IN BRAIN TUMORS

The beneficial effect of steroids in metastatic tumors is often much more dramatic than with primary infiltrating gliomas.

Dexamethasone (Decadron®) dose for brain tumors (*see* *page 33* for cautions):

- for patients not previously on steroids:
  - adult: 10 mg IVP loading, then 6 mg PO/IVP q 6 hrs[11, 12]. In cases with severe vasogenic edema, doses up to 10 mg q 4 hrs may be used
  - peds: 0.5-1 mg/kg IVP loading, then 0.25-0.5 mg/kg/d PO/IVP divided q 6 hrs. NB: avoid prolonged treatment because of growth suppressant effect
- for patients already on steroids:
  - for acute deterioration, a dose of approximately double the usual dose should be tried
  - for "stress doses", *see page 32*

PROPHYLACTIC ANTICONVULSANTS WITH BRAIN TUMORS

PRACTICE GUIDELINE 21-1 PROPHYLACTIC ANTICONVULSANTS WITH BRAIN TUMORS

Level I[13]: prophylactic AEDs should not be used routinely in patients with newly diagnosed brain tumors

Level II[13]: in patients with brain tumors undergoing craniotomy, prophylactic AEDs may be used, and if there has been no seizure, it is appropriate to taper off AEDs starting 1 week post-op

20-40% of patients with a brain tumor will have had a seizure by the time their tumor is diagnosed[13]. Antiepileptic drugs **(AEDs)** are indicated in these patients. 20-45% more will ultimately develop a seizure[13]. *Prophylactic* AEDs do not provide substantial benefit (reduction of risk > 25% for seizure-free survival) and there are significant risks involved.

CHEMOTHERAPY FOR BRAIN TUMORS

Some agents used for CNS tumors are shown in *Table 21-3*[14, 15].

Nitrosoureas: Excellent BBB penetration (*see below*). Significant hematopoietic, pulmonary and renal toxicity.

Blood-brain barrier (BBB):

Traditionally, the BBB has been considered to be a major hindrance to the use of chemotherapy for brain tumors. In theory, the BBB effectively excludes many chemotherapeutic agents from the CNS, thereby creating a "safe haven" for some tumors, e.g. metastases. This concept has been challenged[16]. Regardless of the etiology, the response of most brain tumors to systemic chemotherapy is usually very modest, with a no-table exception being a favorable response of oligodendrogliomas (*see page 611*). Considerations regarding chemotherapeutic agents in relation to the BBB include:

1. some CNS tumors may partially disrupt the BBB, especially malignant gliomas[17]
2. lipophilic agents (e.g. nitrosoureas) may cross the BBB more readily
3. selective intraarterial (e.g. intracarotid) injection[18]: produces higher local concentration of agents which increases penetration of the BBB, with lower associated systemic toxicities than would otherwise occur
4. the BBB may be iatrogenically disrupted (e.g. with mannitol) prior to administration of the agent
5. the BBB may be bypassed by intrathecal administration of agents via LP or ventricular access device (e.g. methotrexate for CNS lymphoma, *see page 675*)
6. biodegradable polymer wafers containing the agent may be directly implanted (*see page 601*)

Table 21-3 Chemotherapeutic agents used for CNS tumors

Agent	Mechanism

1. nitrosoureas: BCNU (carmustine), CCNU (AKA lomustine), ACNU (nimustine)	DNA crosslinks, carbamoylation of amino groups
2. alkylating (methylating) agents (procarbazine, temozolomide - *see page 602*)	DNA alkylation, interferes with protein synthesis
3. carboplatin, cisplatin	chelation via intrastrand crosslinks
4. nitrogen mustards: cyclophosphamide, isofamide, cytoxan	DNA alkylation, carbonium ion formation
5. vinca alkaloids: vincristine, vinblastine, paclitaxel	microtubule function inhibitors
6. epidophyllotoxins (ETOP-oside, VP16, teniposide, VM26)	topoisomerase II inhibitors
7. topotecan, irinotecan (CPT-11)	topoisomerase I inhibitors
8. tamoxifen	protein kinase C inhibitor
9. bevacizumab (Avastin®)	anti-VEGF antibody may be useful in vestibular neuromas (*see page 624*)
10. hydroxyurea 11. bleomycin 12. taxol (paxlitaxol) 13. methotrexate 14. cytosine, arabinoside 15. corticosteroids: dexamethasone, prednisone 16. fluorouracil (FU)	

CAT SCAN FOLLOWING SURGICAL REMOVAL OF TUMOR

To assess degree of tumor removal, a post-op brain CT without and with contrast should either be obtained within 2-3 days[19], or should be delayed at least ≈ 30 days. The non-contrast scan is important in the early post-op period to determine which areas of increased intensity are due to post-op blood and not enhancement. The contrast CT demonstrates areas of enhancement, which may represent residual tumor. After ≈ 48 hours, contrast enhancement due to post-operative inflammatory vascular changes ensues, which may be impossible to differentiate from tumor. This usually subsides by ≈ 30 days[20], but may persist for 6-8 weeks[21]. This recommendation regarding the timing of post-op CT does not apply to pituitary tumors (see *Pituitary tumors*, page 633). The effect of steroids on contrast enhancement is controversial[22, 23], and may depend on many factors (including tumor type).

POSTERIOR FOSSA (INFRATENTORIAL) TUMORS

See *Posterior fossa lesions* on page 1209 for differential diagnosis (includes non-neo-plastic lesions as well).

EVALUATION

In pediatric patients with a posterior fossa tumor, an MRI of the lumbar spine should be done pre-op to rule-out drop mets (post-op there may be artifact from blood).

In adults, most intraparenchymal p-fossa tumors will be metastatic, and work-up for a primary should be undertaken (*see page 706*).

TREATMENT OF ASSOCIATED HYDROCEPHALUS

In cases with hydrocephalus at the time of presentation, some authors advocate initial placement of VP shunt or EVD prior to definitive surgery (waiting ≈ 2 wks before surgery) because of possibly lower operative mortality[24]. Theoretical risks of using this approach include the following:

1. placing a shunt is generally a lifelong commitment, whereas not all patients with hydrocephalus from a p-fossa tumor will require a shunt
2. possible seeding of the peritoneum with malignant tumor cells e.g. with medulloblastoma. Consider placement of tumor filter (may not be justified given the high rate of filter occlusion and the low rate of "shunt metastases"[25])
3. some shunts may become infected prior to the definitive surgery
4. definitive treatment is delayed, and the total number of hospital days may be increased
5. upward transtentorial herniation (*see page 285*) may occur if there is excessively rapid CSF drainage

Either approach (shunting followed by elective p-fossa surgery, or semi-emergent definitive p-fossa surgery) is accepted. At Children's Hospital of Philadelphia, dexamethasone is started and the surgery is performed on the next elective operating day, unless neurologic deterioration occurs necessitating emergency surgery[26].

Many surgeons place a ventriculostomy at the time of surgery (*see page 156*). CSF is drained only after the dura is opened to help equilibrate the pressures between the infra- and supratentorial compartments. Post-op, the external ventricular drain is usually set at a low height (≈ 10 cm above the EAM) for 24 hours, and is progressively raised over the next 48 hrs and should be D/C'd by ≈ 72 hrs post-op.

21.2. Primary brain tumors

21.2.1. Low grade gliomas

This special section is included here because the following tumors are sometimes grouped together despite the fact that they have different cell lineages.

Cell lineages considered under the heading of low-grade gliomas **(LGG)** include:

1. WHO grade II infiltrating astrocytoma (fibrillary or protoplasmic) (*see page 595*) } comprise most low grade gliomas in adults
2. oligodendroglia (*see page 609*) } comprise most low grade gliomas in adults
3. mixed astrocytes & oligodendroglia (oligoastrocytoma) } comprise most low grade gliomas in adults
4. gangliogliomas (*see page 677*) } less frequent histologies
5. gangliocytomas } less frequent histologies
6. juvenile pilocytic astrocytoma (*see page 603*)} less frequent histologies
7. pleomorphic xanthoastrocytomas (*see below*)} less frequent histologies
8. dysembryoplastic neuroepithelial tumors **(DNT)** (*see below*)} less frequent histologies

Spatial definition[27, 28]

Can be used to classify LGG into 3 types (independent of histologic group).

- Type 1: solid tumor only without infiltration of brain parenchyma. Most amenable to surgical resection. Most favorable prognosis. Includes gangliogliomas, pilocytic astrocytomas, pleomorphic xanthoastrocytomas, and some protoplasmic astrocytomas (no oligodendrogliomas are in this group)
- Type 2: solid tumor associated with surrounding tumor-infiltrated brain parenchyma. Surgical resection may be possible, depending on tumor location. Often low-grade astrocytomas
- Type 3: infiltrative tumor cells without solid tumor tissue. Risk of neurologic deficit may preclude surgical resection. Usually oligodendrogliomas

Clinical

Although there are differences among the specific histological types, these tumors generally occur in young adults or children, and are often diagnosed after a history of seizures.

Neuroradiology

MRI: Most LGG are hypointense on T1WI. T2WI shows high signal changes that extend beyond the tumor volume demonstrated on other imaging sequences[28]. Only ≈ 30% enhance.

PET scans: usually shows reduced uptake of fluorodeoxyglucose compared to the rest of the brain, indicative of hypometabolism.

Diagnosis

Although imaging (and clinical) characteristics may suggest one specific tumor type, biopsy is usually required to definitively determine the diagnosis.

Treatment

Complete surgical excision is often sufficient for some of these tumors when it can be accomplished (e.g. with cystic cerebellar pilocytic astrocytomas **(PCAs)**). When this is not possible (e.g. with most hypothalamic PCAs and PCAs involving the optic nerves and chiasm), then further therapy is required, usually in the form of chemotherapy for younger children[29] (to defer the need for XRT until the patient is as old as possible).

DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMORS (DNT) OR (DNET)[30, 31]

Epidemiology

Incidence: not accurately known because the diagnosis may be missed. Estimated range: 0.8-5% of all primary brain tumors. Typically occurs in children and young adults.

Most common locations: temporal or frontal. Parietal and especially occipital lobe involvement is rare. DNTs have been reported in the cerebellum, pons & basal ganglia.

Clinical

Typically associated with longstanding medically intractable seizures, usually complex partial. Symptoms usually begin before age 20.

Imaging

Cortical lesions with no surrounding edema and no midline mass effect.

CT: hypodense with distinct margins. Deformity of overlying calvaria is common.

MRI: T1WI: hypointense. T2WI: hyperintense, septations may be seen. If there is enhancement, it is usually nodular.

PET scan: hypometabolic with [18F]-fluorodeoxyglucose. Negative [11C]-methionine uptake (unlike all other gliomas).

Pathology

A WHO Grade I glioma. Thought to arise embryologically from the secondary germinal layer (which includes subependymal layer, cerebellar external granular layer, hippocampal dentate fascia & subpial granular layer).

Multinodularity at low-power is a key feature, and the primary constituent cells are oligodendrocytes and to a lesser extent, astrocytes that are often pilocytic. Occasionally difficult to differentiate from oligodendroglioma.

Two distinct forms[32] (do not appear to have different prognoses):

1. simple form: glioneural elements consisting of axon bundles perpendicular to the cortical surface, lined with oligodendroglial-like cells that are S-100 positive and GFAP negative. Normal appearing neurons floating in a pale eosinophilic matrix are scattered between these columns (no resemblance to ganglion cells, unlike gangliogliomas)
2. complex form: glioneural elements as described above in the simple form, with glial nodules scattered throughout. The glial component may mimic a low-grade fibrillary astrocytoma. Foci of cortical dysplasia occur

Outcome

Seizure control: usually improves after surgery. Degree of control seems to correlate with completeness of removal. Improvement in seizures correlates inversely with the duration of intractable seizures.

Recurrence/continued growth: recurrence after complete removal, or tumor

growth after partial resection is rare. Adjuvant treatment (XRT, chemotherapy…) is of no benefit. Mitoses or endothelial proliferation, seen on occasion, do not affect outcome. Malignant transformation is very rare.

PLEOMORPHIC XANTHOASTROCYTOMA (PXA)

Key concepts:

- low-grade glioma, possibly from subpial astrocytes → superficial location, > 90% supratentorial, most common in children or young adults
- mural nodule with cystic component in 25%, meninges involved in > 67%
- pathology: pleomorphic cells (xanthomatous (lipid laden) cells, fibrillary and giant multinucleated astrocytes). Usually circumscribed, occasionally invasive
- WHO grade II unless high mitotic index or necrosis, which is WHO grade III
- treatment: maximal safe resection. XRT or chemo ≈ only for grade III

A low-grade glioma thought to arise from subpial astrocytes which may explain their superficial location and abundance of reticulin fibers. Over 90% are supratentorial. Predilection for temporal lobes (50%), followed by parietal, occipital & frontal lobes. Most have a cystic component (may be multiloculated, but > 90% have a large, single cyst).

Epidemiology:≈ 1% of astrocytomas. Usually occurs in children or young adults (most are < 18 years age). No gender difference.

Clinical: Usual presentation: seizures. May also produce focal deficit or increased ICP.

Imaging: The cyst, when present, may partially enhance on CT or MRI. A mural nodule is present in 25%. May have "dural tail" (67% show leptomeningeal involvement, 13% show involvement of all 3 meningeal layers). Peritumoral edema may be mild to moderate, calcifications are rare[33].

CT: solid portion of tumor is ill-defined and may be isodense to grey matter.

MRI: T1WI: hypointense cystic component with ill defined isointense solid component that strongly enhances with gadolinium. T2WI: hyperintense cystic component with ill-defined isointense solid component.

Pathology: WHO grade II (MIB is usually < 1%) unless there is a high mitotic index or necrosis which qualifies as WHO grade III "PXA with anaplastic

features"[34]. Compact, superficial tumor with marked cellular pleomorphism (fibrillary and giant multinucleated astrocytes, large xanthomatous (lipid laden) GFAP staining cells (bespeaking glial origin)), abundant reticulin and frequent perivascular chronic inflammatory cells. The reticulin fibers surround two cell types:

1. spindle cells: fusiform cell shape with elongate nuclei
2. pleomorphic cells: round cells with heterochromic, pleomorphic nuclei that may be mononucleated or multinucleated. Variable intracellular lipid content

Usually circumscribed, occasionally infiltrates cortex. Marked cellular pleomorphism may cause these tumors to be mistaken for anaplastic astrocytoma. Vascular proliferation and necrosis are absent[35], most but not all lack mitotic figures. Some PXAs undergo anaplastic change[36]. There have also been several reported cases of malignant transformation to anaplastic astrocytoma or glioblastoma[37].

Differential diagnosis:

1. imaging: meningioma is also superficial with dural tail, may also resemble low grade fibrillary astrocytoma
2. pathology: may be confused with anaplastic astrocytoma

Treatment:

1. surgery: primary treatment
   A. gross total resection if it can be accomplished without unacceptable neurologic deficit, otherwise subtotal resection
   B. extent of resection: most strongly associated with recurrence free survival[38]
   C. incomplete resections should be followed since these tumors may grow very slowly over many years before retreatment is necessary, and repeat excision should be considered
2. radiation therapy: controversial
   A. literature suggests either no difference in overall survival or possibly a trend toward prolonged survival[35]
   B. considered with: residual disease, high mitotic index, or necrosis
3. chemotherapy: role not defined

Prognosis: Overall survival with gross total resection or subtotal resection, with or without radiation and chemotherapy: 5 years = 80%, 10 years = 71%[34].

Extent of resection, mitotic index, and necrosis appear to be the best predictors of outcome[33, 38].

DYSPLASTIC GANGLIOCYTOMA OF CEREBELLUM (LHERMITTE-DUCLOS DISEASE)

AKA: ganglioneuroma of the cerebellum, purkinjoma, granular cell hypertrophy of the cerebellum, gangliocytoma dysplasticum, hamartoma of the cerebellum.

Rare (200 case reports[39]) cerebellar lesion with features of both a malformation and a low grade (WHO I) neoplasm that has the propensity to progress (enlarge) and recur after surgery. May be focal or diffuse. Diffuse enlargement of cerebellar folia.

Strongly associated with **Cowden syndrome**: AKA multiple hamartoma syndrome. Autosomal dominant. Incidence: 1 in 250,000 live births[40]. Associated with thyroid, breast & uterine Ca, mucosal neuromas & meningiomas).

Histology: Derangement of normal laminar cellular architecture of the cerebellum with:

1. thickening of the outer molecular cell layer
2. loss of middle Purkinje cell layer
3. infiltration of inner granular cell layer with dysplastic ganglion cells

Clinical: Typically a middle aged <u>adult</u> with signs and symptoms of a cerebellar mass. May also present with hydrocephalus or may be an incidental finding.

Imaging:

CT: hypo- to isodense, nonenhancing lesion with mass effect.

MRI: T1WI: hypo- to isointense. T2WI: hyperintense, heterogeneous. Nonenhancing. Characteristic striated appearance[41] (tiger stripes) due to widened cerebellar folia. May contain calcifications. DWI: hyperintense. ADC map: hypointense.

NB: in a child with MRI findings of Lhermitte-Duclos disease **(LDD)** (even if classic), a medulloblastoma is statistically more likely[42, 43] (especially medulloblastoma with extensive nodularity[44] **(MBEN)**).

Treatment: Controversial. A few cases with a benign course have been described[45]. Shunting for hydrocephalus. Biopsy is recommended[43] particularly for pediatric cases to rule-out medulloblastoma. Surgical excision may be

considered when there is significant mass effect[46]. Efficacy of XRT is unknown.

21.2.2. Astrocytoma

The most common primary intra-axial brain tumor, ≈ 12,000 new cases/year in the U. S.

CLASSIFICATION BY CELL TYPE

The dominant cell types of astrocytomas allows their classification into one of the subdivisions shown in *Table 21-4*. The rationale for separating "ordinary" from "special" astrocytomas is based on a much different and more favorable behavior of the latter group which does not depend on grade within that group (these also tend to occur in younger patients). The notion that pilocytic and microcystic cerebellar astrocytomas are the same tumor as fibrillary astrocytomas but in a different location has been abandoned (see *Pilocytic astrocytomas*, page 603).

Table 21-4 Classification of astrocytomas by cell type

"Ordinary" astrocytomas	"Special" astrocytomas
fibrillary gemistocytic protoplasmic	pilocytic microcystic cerebellar subependymal giant cell

Gemistocytic astrocytomas: Gemistocytes are plump cells filled with eosinophilic, hyaline cytoplasm, seen almost exclusively in gemistocytic astrocytomas and GBM. Small numbers, however, may be seen in fibrillary astrocytomas (gemistocytes should account for > 20% of tumor cells for an astrocytoma to be considered a gemistocytic astrocytoma). Gemistocytic astrocytomas are comprised primarily of these cells, but rarely occur in pure form. Often meet grade III (malignant astrocytoma) criteria.

21.2.2.1. "Ordinary" astrocytomas

"Ordinary" here is meant to encompass Grade II-IV infiltrating astrocytomas, and to exclude special more-circumscribed astrocytomas such as pilocytic astrocytoma.

GRADING AND NEUROPATHOLOGY

Grading of astrocytomas remains controversial. Some special concerns:

1. sampling error: may have different degrees of malignancy in different

areas
2. dedifferentiation: tumors tend to progress in malignancy over months or years (see *Dedifferentiation*, page 595)
3. histological criteria that affect prognosis include: cellularity, presence of giant cells, anaplasia, mitosis, vascular proliferation with or without endothelial proliferation, necrosis, and pseudopalisading[47]
4. in addition to histology, issues that affect clinical behavior include:
   A. patient age
   B. extent of tumor
   C. topography: tumor location, especially in relation to critical structures

NEUROPATHOLOGICAL GRADING

Kernohan system

The obsolete Kernohan system[49] divided these tumors into 4 grades (grade IV AKA glioblastoma multiforme) based on the degree of presence of a number of features such as anaplasia, nuclear pleomorphism, number of mitoses… Prognostically, this system distinguished only 2 clinically different groups (grades I/II, and grades III/IV) and is not used today. It is presented for completeness when reviewing older literature.

Table 21-5 Approximate equivalence of Kernohan grade (I-IV) to WHO system

Kernohan	**WHO designation**[48]	
	I more circumscribed tumors: e.g. pilocytic astrocytomas	
I II	} II: diffuse astrocytoma (low-grade)	
III	III: anaplastic astrocytoma	} malignant astrocytoma
IV	IV: glioblastoma	

Current grading systems

The 2 main systems is use today are shown below, and differ primarily in the definition of Grade I.

WHO system: The World Health Organization **(WHO)** system is shown in *Table 21-5*[48]. In the WHO system, grade I is reserved for special types of astrocytomas that are more circumscribed, including pilocytic astrocytomas (see

Low grade gliomas, page 590), while the more typical astrocytic neoplasms are graded II through IV. The approximate equivalence to the Kernohan grade is also shown.

St. Anne/Mayo grading system: The classification system known as the St. Anne/Mayo **(SA/M)** system[50] addresses histological considerations, and is reproducible and prognostically significant[51]. It is restricted to "ordinary" astrocytomas, as grade has not been shown to correlate with clinical behavior in pilocytic astrocytomas. It is similar to the WHO system except that SA/M grade I astrocytomas are a very rare diffuse astrocytoma without atypia[48].

Table 21-6 WHO classification of ("ordinary") astrocytic tumors

Designation	Criteria
II: diffuse astrocytoma	cytological atypia alone
III: anaplastic astrocytoma	anaplasia and mitotic activity
IV: glioblastoma (GBM)	also show microvascular proliferation and/or necrosis

The SA/M system assesses the presence or absence of 4 criteria (*see Table 21-7*) and then assigns a grade based on the number of criteria present (*see Table 21-8*). When the presence of any criteria is uncertain, it is considered to be absent.

The criteria tended to occur in a predictable sequence: nuclear atypia occurred in all grade 2 tumors, mitotic activity was seen in 92% of grade 3 tumors (and in none of the grade 2 tumors), necrosis and endothelial proliferation were restricted almost only to grade 4 tumors (they were seen in only 8% of grade 3 tumors).

The frequencies among 287 astrocytomas were: grade 1 = 0.7%, grade 2 = 16%, grade 3 = 17.8%, and grade 4 = 65.5%.

Median survival was as follows[50]: (there were only two grade 1 patients, one survived 11 years and the other was still alive after 15 years), grade 2 = 4 years, grade 3 = 1.6 years, and grade 4 = 0.7 years (8.5 months).

Table 21-7 St. Anne/Mayo criteria

• nuclear atypia: hyperchromatasia and/or obvious variation in size and shape
• mitoses: normal or abnormal configuration
• endothelial proliferation: vascular lumina are surrounded by "piled-up" endothelial cells. Does not include hypervascularity
• necrosis: only when obviously present. Does not include pseudopalisading when seen alone

Relative frequency of astrocytoma grades

Ratio of (glioblastoma):(anaplastic astrocytoma):(low-grade astrocytoma) is ≈ 5:3:2. Peak age incidence rises with increasing grade: 34 years for low-grade astrocytoma, 41 years for anaplastic astrocytoma, and 53 years for GBM[52].

Low-grade astrocytoma (WHO II)

AKA **low-grade diffuse astrocytoma**. Three cell types:

1. fibrillary astrocytoma: the most common histological subtype of Grade II
2. gemistocytic astrocytoma: particularly prone to progress to Grade II & IV
3. protoplasmic astrocytoma

Table 21-8 St. Anne/Mayo grade

Grade	No. of criteria
1	0
2	1
3	2
4	3 or 4

These tumors tend to occur in children and young adults. Most present with seizures. There is a predilection for temporal, posterior frontal and anterior parietal lobes[53]. They demonstrate low degrees of cellularity and preservation of normal brain elements within the tumor. Calcifications are rare. Anaplasia and mitoses are absent (a single mitosis is allowed). Blood vessels may be slightly increased in number. The ultimate behavior of these tumors is usually not benign. The most important favorable prognosticator is young age. Poor prognosis is associated with findings of increased ICP, altered consciousness, personality change, significant neurologic deficits[54], short duration of symptoms before diagnosis, and enhancement on imaging studies. Also *see page 590*.

Dedifferentiation: The major cause of morbidity with low-grade astrocytomas is dedifferentiation to a more malignant grade. Low grade fibrillary astrocytomas tend to undergo malignant transformation more quickly (with six-fold increased rapidity) when diagnosed after age 45 years than when diagnosed earlier[52] (*see Table 21-9*). Gemistocytic astrocytomas tend to dedifferentiate more rapidly than fibrillary astrocytomas. > 60% of fibrillary astrocytomas have a mutation of the TP53 gene located on chromosome 17p; these tumors are more likely to dedifferentiate. Once dedifferentiation occurs, median survival is 2-3 years

beyond that event. Genetic markers that correlate with a higher degree of malignant degeneration include:

1. loss of heterozygosity on chromosomes 10 & 17
2. alteration in tumor suppressor genes at 9p, 13q, 19q & 22q
3. changes in epidermal growth factor receptor (EGRF) and platelet-derived growth factor (PDGF)
4. transformation of the p[53] suppressor gene

Table 21-9 Dedifferentiation rate for low grade astrocytomas

	Patients diagnosed @ age < 45 yrs	Patients diagnosed @ age≥45 yrs
mean time to dedifferentiation	44.2 ± 17 mos	7.5 ± 5.7 mos
time to death	58 mos	14 mos

Malignant astrocytomas (WHO III & IV)

This category encompasses anaplastic astrocytoma **(AA)** and glioblastoma **(GBM)**. Although both are “malignant”, AA and GBM have distinct differences. Among 1265 patients with malignant astrocytomas, the mean age was 46 yrs for AA, and 56 yrs for GBM. Mean duration of symptoms pre-op: 5.4 mos for GBM, and 15.7 mos for AA. Malignant astrocytomas may develop from low grade astrocytomas via dedifferentiation (*see above*), however they may also arise de novo.

Glioblastoma (multiforme) (WHO IV): The most common primary brain tumor, it is also the most malignant astrocytoma. Current nomenclature omits “multiforme”[5].

Primary vs. secondary glioblastoma[2]: most GBM arise de novo (primary), others progress from less malignant astrocytomas (secondary). Although they evolve from different genetic precursors, there is no reliable distinguishing histopathologic marker, and the difference in prognosis and response to different therapies is unknown.

- **primary glioblastoma**: the majority of GBMs. Arise without evidence (clinical or histological) of a less malignant precursor. More common in older patients (mean age = 55 years) after a short (< 3 month) clinical history. Characterized by *EGFR* amplification (≈ 40% of cases) and/or overexpression (60%), *PTEN* mutations (30%), *p[16]INK4a* deletion (30–40%), *MDM2* amplification (< 10%), and/or overexpression (50%), and in 50–80% of cases, loss of heterozygosity **(LOH)** on the entire chromosome

- **secondary glioblastoma**: develop by malignant degeneration of WHO grade II or III astrocytoma. Patients are younger (mean age = 40 years) and have a slower clinical course. 60% have *TP53* mutations (> 90% of these are evident in the less malignant precursors). Malignant degeneration is characterized by allelic loss of chromosomes 19q and 10q

Histological findings associated with GBM (not all may be present, and this list does not follow any of the standard grading systems above):

- gemistocytic astrocytes
- neovascularization with endothelial proliferation
- areas of necrosis
- pseudopalisading around areas of necrosis

Infratentorial glioblastoma **(GBM)** is rare, and often represents subarachnoid dissemination of a supratentorial GBM (used as an argument for irradiation in all patients with p-fossa GBM)[55].

Miscellaneous pathological features

Glial fibrillary acidic protein (GFAP): Most astrocytomas stain positive for GFAP (however, may not stain positive in some poorly differentiated gliomas, and in purely gemistocytic astrocytomas since fibrillary astrocytes are required to be positive).

Cysts: Gliomas may have cystic central necrosis, but may also have an associated cyst even without necrosis. When fluid from these cysts is aspirated it can be differentiated from CSF by the fact that it is usually xanthochromic and often clots once removed from the body (unlike e.g. fluid from a chronic subdural). Although they may occur with malignant gliomas, cysts are more commonly associated with pilocytic astrocytomas (*see page 604*).

MIB-1 index: (*see page 720*). It has been suggested that a MIB-1 index ≥ 7-9% is indicative of an anaplastic tumor, while MIB-1 < 5% favors a low-grade tumor. However, variability between observers and institutions precludes using the MIB-1 index as a sole discriminant between grade II & III astrocytomas[2].

Neuroradiological grading and findings

Astrocytomas typically arise in white matter (e.g. centrum semiovale) and traverse through white matter tracts (*see below*). For MR-spectroscopy findings, *see page 133*.

Table 21-10 Grading gliomas by CT or MRI

Kernohan grade	Typical radiographic findings	
I	CT: low density MRI: abnormal signal on T2WI	no mass effect, no enhancement
II		mass effect, no enhancement
III	complex enhancement*	
IV	ring enhancement (central necrosis or cyst)	

* however, some may not enhance

CT scan & MRI grading

Grading gliomas by CT or MRI is imprecise[56], but may be used as a preliminary assessment (*see Table 21-10*). Neuroradiologic grading is not applicable to pediatric patients or special astrocytomas (e.g. pilocytic astrocytomas).

Low grade gliomas: usually hypodense on CT. Most are hypointense on T1WI MRI, and show high intensity changes on T2WI that extend beyond the tumor volume. Most do not enhance on CT or MRI (although up to 40% do[57], and these may have a worse prognosis). The UCSF preoperative grading system for low-grade infiltrating gliomas[58] assigns 1 point for the presence of each of 4 parameters shown in *Table 21-11*. The points are summed and the prognosis is shown in *Table 21-12* (this scale needs to be validated at other institutions). Another study found poor prognosis associated with: age ≥ 40 years, tumor ≥ 6 cm dia, tumor crossing midline and the presence of neurologic deficit[59].

Table 21-11 Preoperative grading of low-grade gliomas[58]

Item	Yes/No
age > 50 years	Yes = 1, No = 0
KPS* ≤ 80	Yes = 1, No = 0
located in eloquent brain†	Yes = 1, No = 0
maximal diameter > 4 cm	Yes = 1, No = 0

* KPS = Karnofsky performance score (page 1182)

† for this study, eloquent brain is defined as any of: primary sensory or motor cortex, Wernicke’s or Broca’s area, basal ganglia/internal capsule, thalamus or primary visual cortex

Table 21-12 Sum of points from *Table 21-11*

Sum	5-year survival	5-year progression-free survival
0-1	97%	76%
2	81%	49%
3-4	56%	18%

Malignant gliomas: anaplastic astrocytomas **(AA)** may not enhance[60] (31% of highly anaplastic and 59% of moderately anaplastic astrocytomas do not enhance on CT[61] (MRI not studied)). Calcifications and cysts occur in 10-20% of AA[60]. Most glioblastomas enhance, but some rare ones do not[56, 61].

Ring-enhancement with glioblastoma (GBM): The nonenhancing center may represent necrosis or associated cyst (*see above*). The enhancing ring is cellular tumor, however, tumor cells also extend ≥ 15 mm beyond the ring[62].

Positron emission tomography (PET) scan

Low grade fibrillary astrocytomas appear as hypometabolic "cold" spots with fluorodeoxyglucose PET scans. Hypermetabolic "hot" spots suggest high-grade astrocytomas.

Angiographic appearance

AA's usually appear as an avascular mass. Tumor blush and AV-shunting with early draining veins are more characteristic of GBM.

SPREAD

Gliomas may spread by the following mechanisms[63] (note: < 10% of recurrent gliomas recur away from the original site[64]):

1. tracking through white matter
    A. corpus callosum **(CC)**
        1. through genu or body of CC → bilateral frontal lobe involvement ("**butterfly glioma**")
        2. through splenium of CC → bilateral parietal or occipital lobes
    B. cerebral peduncles → midbrain involvement
    C. internal capsule → encroachment of basal ganglion tumors into centrum semiovale
    D. uncinate fasciculus → simultaneous frontal and temporal lobe tumors

    E. interthalamic adhesion → bilateral thalamic gliomas
2. CSF pathways (subarachnoid seeding): 10-25% frequency of meningeal and ventricular seeding by high grade gliomas[65]
3. rarely, gliomas may spread systemically

MULTIPLE GLIOMAS

Discussion of multiple gliomatous masses has to acknowledge the concept that astrocytoma is a multifocal disease, not a focal one. Some terms are probably artificial, e.g. since gliomatosis cerebri probably represents a diffuse infiltrating glial tumor with areas that may dedifferentiate into higher grade and then is called multicentric glioma.

Settings in which multiple gliomatous masses are encountered:

1. conventional glioma that has spread by one of the mechanisms previously described (*see above*)
2. **gliomatosis cerebri**: a diffuse, infiltrating astrocytoma that invades almost all of the cerebral hemispheres and brainstem. Usually low-grade[57], areas of anaplasia and glioblastoma may also occur[66] and may present as focal mass[67]. Occurs most frequently in 1st 2 decades
3. multiple primary gliomas: some of the following terms are inconsistently used interchangeably: "multicentric", "multifocal", and "multiple". Reported range of occurrence is 2-20% of gliomas[68, 69] (lower end of range ≈ 2-4% is probably more accurate, the higher end of the range is probably accounted for by infiltrative extension[70 (p 3117)])
    A. commonly associated with neurofibromatosis and tuberous sclerosis
    B. rarely associated with multiple sclerosis and progressive multifocal leukoencephalopathy
4. **meningeal gliomatosis**: dissemination of glioma throughout the CSF, similar to carcinomatous meningitis (*see page 711*). Occurs in up to 20% of autopsies on patients with high-grade gliomas. May present with cranial neuropathies, radiculopathies, myelopathy, dementia, and/or communicating hydrocephalus

In a series of 25 patients with multicentric glioma[71], glioblastoma was the most common pathology (48%), followed by anaplastic astrocytoma (20%), and glioblastoma with simultaneous AA (20%).

TREATMENT CONSIDERATIONS FOR MULTIPLE GLIOMAS

There is little data available. In a nonrandomized study of 25 patients with multi-focal glioma[71], the 16 patients who underwent debulking did better than the 9 who did not. However, there was significant selection bias in choosing patients suitable for craniotomy.

Biopsy is generally required/recommended to confirm the diagnosis.

Σ Once the diagnosis of multiple gliomatous masses has been ascertained, local therapies (e.g. surgery, interstitial radiation…) are impractical. Whole brain radiation and possibly chemotherapy are indicated. An exception would be to consider debulking tumor to prevent herniation in a patient deteriorating from mass effect.

TREATMENT

LOW-GRADE ASTROCYTOMAS (WHO GRADE II)

Treatment options:

1. no treatment: follow serial neurologic exams and imaging studies
2. radiation
3. chemotherapy
4. surgery
5. combinations of radiation and chemotherapy, with or without surgery

Analysis

No well-designed study has shown that any approach for supratentorial WHO grade II infiltrating astrocytomas in adults is clearly superior. Some treatments may simply expose the patient to the risk of treatment side effects. These tumors are slow growing, and until progression on imaging or malignant degeneration is documented, it may be no worse to not treat the patient[72]. Although this view has been challenged[73], a definitive study has yet to be performed. The following are associated with more aggressive tumors and should prompt consideration for some form of treatment:

1. extremely young patients, or patients > 50 yrs age (increasing age at diagnosis is associated with more rapid dedifferentiation, see *Dedifferentiation*, page 595)
2. large tumors that enhance (size is one of the most important prognosticators[74])
3. symptomatic patients, especially those with short clinical history
4. evidence of progression on imaging studies

Surgery for low grade gliomas

The role of surgery in low-grade gliomas is controversial, due in part to the fact that surgery is not curative for most infiltrating hemispheric gliomas, and many of these tumors are not completely resectable. There is a trend suggesting that "complete" surgical removal, when possible, is associated with a better prognosis[28, 74]. However, this remains unproven.

Surgery is the principal treatment in the following situations of low-grade astrocytomas:

1. surgical biopsy or partial resection is recommended <u>in almost all cases</u> to establish the diagnosis since clinical and radiographic data are not definitive[53]
2. pilocytic astrocytomas
   A. cerebellar tumors occurring in children & young adults (*see page 604*)
   B. supratentorial pilocytic astrocytomas
3. when herniation threatens from large tumors or tumor cysts
4. tumors causing obstruction of CSF flow
5. may help in seizure control with refractory seizures
6. in an attempt to delay adjuvant therapy and its side-effects in children (especially XRT in those < 5 yrs old)[53]
7. smaller tumors are less aggressive than large ones[75] and may be better candi-dates for early surgery (also, *see below*)

The role of surgery is limited in the following situations of low-grade astrocytomas:

1. disseminated (poorly circumscribed) tumors
2. multifocal tumors
3. location in eloquent brain

Technical considerations at surgery:

Since the margins of low-grade gliomas may not be readily visible at the time of surgery, adjuncts such as stereotactic and image guided techniques may be advantageous for deep tumors or in areas bordering on eloquent brain[76]. Awake surgery is an option for tumors bordering on eloquent brain.

<u>Unresolved</u> issues: whether the extent of tumor removal influences 1) time to tumor progression, 2) incidence of malignant degeneration, and 3) period of survival. One series[77] suggested that 5-year survival improved from 50% with incomplete resection to 80% with complete resection. Early radical surgery may

reduce the rate of malignant degeneration, especially when tumor volume is < 30 ml[53].

Radiation therapy (XRT) for low grade gliomas

Background: Early XRT increases progression-free survival **(PFS)** and seizures, but has no effect on overall survival **(OS)**[78]. Following incomplete resection, retrospective evidence suggests that PFS and OS are prolonged by XRT[79]. Two prospective trials found no difference in OS or PFS between different XRT doses (EORTC trial[74]: 45 Gy in 5 weeks vs. 59.4 Gy in 6.6 weeks; Intergroup study[80] 50.4 vs. 64.8 Gy). Side effects from WBXRT include: leukoencephalopathy & cognitive impairment (see *Radiation injury and necrosis*, page 771). The frequency of side effects may[80] or may not[81] increase at higher XRT doses.

Recommendations for XRT in low-grade gliomas (modified[82]):

1. dogmatic statements regarding XRT are unwarranted
2. when considered for use as a primary treatment, XRT may be best reserved for patients who are more likely to progress (older patients, involvement of corpus callosum). Dosage: **45-54 Gy** (NCCN guidelines). Expectant management may be a better course for younger patients with asymptomatic lesions
3. in cases of gross total surgical removal, or incomplete removal in cases of pilocytic astrocytoma or cystic cerebellar astrocytoma, XRT may be withheld until tumor recurrence or progression that cannot be treated surgically is documented
4. in cases of incomplete removal of ordinary low-grade astrocytomas, post-op XRT may be considered, consisting of fractionated treatments to a maximum of **45 Gy** to the tumor bed plus surrounding margin (2 cm for enhancing, and 1 cm around hypodense zone for nonenhancing tumors) instead of whole brain XRT
5. malignant degeneration of tumor should be treated with XRT, following reoperation when appropriate

Chemotherapy for low grade gliomas

Usually reserved for tumor progression. PCV (procarbazine, CCNU, and vincristine) frequently stabilizes tumor growth. Temozolomide (Temodar®) may be effective in progressive WHO grade II astrocytomas (off label use)[83].

Stereotactic biopsy

Due to sampling error, stereotactic biopsy may underestimate the occurrence of GBM by as much as 25%.

Indications for stereotactic biopsy (instead of initial resection) in suspected malignant astrocytomas[84]:

1. tumors located in eloquent or inaccessible areas of brain
2. small tumors with minimal deficit
3. patients in poor medical condition precluding general anesthesia
4. to ascertain a diagnosis when one is not definitely established (including when considering a more definitive operation). Some CNS lymphomas mimic GBM radiographically (and without immunostaining, some have also been mistaken pathologically) biopsy should be given serious consideration (to avoid operating on a lymphoma)

Technique: Yield of biopsy is highest when targets within the low density (necrotic) center and enhancing rim are chosen[62].

Outcome: In a study of 91 cases of malignant gliomas with "critical location" (i.e. deep, midline, or near eloquent brain), it was found that cytoreductive surgery may not improve survival (a limited number of patients underwent cytoreductive surgery with no obvious improvement in survival, but too few to tell if statistically significant), and that biopsy + XRT may be appropriate therapy for these non-lobar malignant tumors (*see Table 21-13*). There was no significant difference in survival between AA and GBM when the tumors were not lobar. A Karnofsky rating $\geq$ 70 at presentation also portends a better prognosis (not statistically significant in this study).

Patients with left-sided tumors and dysphasia are at significant risk of worsening of language function following stereotactic biopsy (the risk of deterioration is low if there is no dysphasia before biopsy)[85].

Table 21-13 Survival after stereotactic Bx*
(91 patients with malignant astrocytoma[84])

Location	Tumor type	Number	Treatment	Median survival (weeks)
deep or lobar	GBM & AA	26 GBM + 4 AA	Bx only (no XRT)	≤ 11
deep	AA	6	Bx + XRT	19.4†
	GBM	22	Bx + XRT	27†
lobar	AA	17	Bx + XRT	129
	GBM	16	Bx + XRT	46.9

* abbreviations: Bx = biopsy; XRT = radiation therapy in adequate dose, defined as 50-60 Gy

† difference not statistically significant

Surgery for high grade gliomas

Cytoreductive surgery followed by external beam radiation (40 Gy whole-brain + 15-20 Gy to the tumor bed delivering a total of ≈ 60 Gy to the tumor) has become the standard against which other treatments are compared[86]. **Elderly patients** (> 65 yrs age): the benefit conferred by surgery is modest (median survival of 17 weeks after biopsy + XRT, versus 30 weeks for surgery + XRT)[87].

Extent of resection: The extent of tumor removal and (in an inverse relationship) the volume of residual tumor on post-op imaging studies have a significant effect on time to tumor progression and median survival[88]. However, while it has been shown that postop residual enhancing tumor is a marker for a worse prognosis (11.8 months median survival if there was enhancing GBM on post-op MRI, 16.7 months if none[89]), it does not follow and has not been proven that being more aggressive to try and remove that last bit of enhancing tissue improves survival[90]. A small randomized study showed improved survival with resection vs. biopsy in elderly patient with GBM[91]. Piepmeir[92] stated it succinctly, "Ultimately, a significant improvement in survival for patients with malignant gliomas will not result from more extensive surgery…".

Alternative views suggest that surgery may be justified to reduce significant mass effect but not for reducing tumor burden[93, 94]. Since these tumors cannot be cured with surgery, the goal should be to prolong quality survival; this can usually be accomplished with tumor excision for lobar gliomas in patients in good neurologic condition.

Partial resection of a GBM carries significant risk of post-operative hemorrhage and/or edema (**wounded glioma syndrome**) with risk of herniation. Furthermore, the benefit of subtotal resection is dubious. Therefore, surgical

excision should only be considered when the goal of gross total removal is feasible.

As a result of the above, the following are usually not candidates for surgical debulking

1. extensive dominant lobe GBM
2. lesions with significant bilateral involvement (e.g. large butterfly gliomas)
3. elderly patients
4. Karnofsky score < 70 (in general, with infiltrating tumors, the neurologic condition on steroids is as good as it is going to get, and surgery rarely improves this)
5. multicentric gliomas

Radiation therapy for high grade gliomas

The usual dose of XRT for malignant gliomas is 50-60 Gy. Whole brain XRT has not been shown to increase survival compared to focal XRT, and the risk of side effects is greater[95].

Brachytherapy has shown no significant benefit as an adjunct to EBRT in the initial treatment of malignant astrocytomas[96].

Stereotactic radiosurgery provided no additional benefit when added to conventional XRT and BCNU chemotherapy[97].

Chemotherapy for high grade gliomas

All agents in use have no more than a 30-40% response rate, and most have 10-20%[98]. Although not positively proven, it appears that the more complete the surgical resection, the more value the chemotherapy has[98]. When given before XRT, chemotherapy may also be useful. There was no survival advantage with combination PCV therapy when added to XRT vs. XRT alone[99].

Alkylating agents produce significant benefit in ≈ 10% of patients[100] (similar efficacy among all available agents: BCNU, CCNU, procarbazine…). Carmustine **(BCNU)** (BiCNU®)[101] and cisplatinum (AKA cisplatin, Platinol®) have been the primary chemo-therapeutic agents used against malignant gliomas. The response may be enhanced by inhibition (via methylation) of the gene responsible for production of the DNA-repair enzyme O6-methylguanine-DNA methyltransferase **(MGMT)**[102].

Σ Following surgery + XRT, median survival is ≈ 9 mos, and 2-year survival is only 5-10%[103]. Meta-analysis showed an absolute increase in 1-year survival of 6% and a 2-month increase in median survival with chemotherapy. Nitrosoureas are fairly well tolerated and easy to administer. However, the quality of life during this modest increase is uncertain, making chemotherapy an option[104].

carmustine (BCNU) (BiCNU®) DRUG INFO

In an attempt to reduce systemic effects, intraarterial injection of carmustine has been tried[105, 106], but side effects are significant, including progressive leukoencephalopathy and visual deterioration due to retinal toxicity (attempts to offset this by selectively injecting distal to the ophthalmic artery have been disappointing). BCNU containing wafers may also be surgically implanted following tumor resection (*see below*).

The only protocol to have been fully validated by Phase 3 study[98] is maximal surgical resection when possible, followed by XRT of 60 Gy, and then BCNU at 6-week intervals of 110 mg/M^2.

Implantable chemotherapy:

Gliadel® wafers: carmustine (BCNU) 7.7 mg in a 200 mg prolifeprosan 20 hydrophobic polymer carrier (wafer). Following tumor removal, up to 8 of the 1.4 cm X 1 mm wafers are applied to the resection bed at the time of surgery. The drug is released over ≈ 2-3 wks. This exposes the tumor to 113 times the concentration of BCNU that could be achieved with systemic administration[107]. In animals, only trace amounts of the drug reach the systemic circulation. FDA approved in the U.S. for implantation in newly diagnosed and recurrent glioblastoma.

Implanting at initial surgery: median survival increased from 11.6 months to 13.8 months in a series of 240 patients with malignant glioma (207 with GBM)[108] when Gliadel® was added to surgical debulking and XRT, and 2-year survival was 16% vs. 8% in the placebo group.

Recurrent malignant glioma: median survival was 28 weeks with BCNU implants compared to 20 weeks with placebo, and 6 month survival was 64% compared to 44% with placebo[109].

No effect on blood counts occurred. The implants do increase cerebral edema, wound healing problems, and the incidence of seizures within 5 days of surgery. 8 wafers cost ≈ $12,500[110].

temozolomide (Temodar® in the U.S., Temodal® globally) **DRUG INFO**

An oral alkylating agent that is given as a prodrug which undergoes rapid non-enzymatic conversion at physiologic pH to the active metabolite monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxic effect of MTIC is associated with alkylation (methylation) of DNA at various sites including the O6 and N7 positions on guanine.

FDA approved for use in adults for:

- the initial relapse of anaplastic astrocytoma and progression of disease while on a regimen containing a nitrosourea (see *Table 21-3*, page 589) and procarbazine
- for newly diagnosed GBM: given as a low dose with concurrent XRT, followed by higher maintenance dose (*see below*)

Has also been used off-label for:

- newly diagnosed AA[111]
- for patients with minimal post-surgery treatment as well as for progressive low grade astrocytomas[83]
- Phase II trials have been published with oligoastrocytoma[112].

Rx for anaplastic astrocytoma: 150 mg/m^2/d PO q d **x** 5 d. Dose for subsequent 5 day cycles every 28 days is adjusted according to nadir neutrophil and platelet counts (which occurs at day 21) during the previous cycle and the start of the next cycle (therefore check CBC on days 21 & 29).

Rx when given concurrently with XRT for newly diagnosed GBM: 75 mg/m^2/d orally on an empty stomach **x** 42 days, 1 hr before XRT (on days without XRT, it is given in the morning)[113]. After completion of XRT, it is given orally as 150 mg/m^2/d on days 1-5 every 28 days for at least 6 cycles.

Side effects: Most common side-effect is N/V which may be ameliorated by pretreatment with ondansetron (Zofran®) 30 minutes before temozolomide dose. Constipation and fatigue are also common. H/A and seizures have been reported. **Supplied**: 5, 20, 100, 140, 180 & 250 mg capsules. 100-mg powder for injection. Cost: $1,300-1,500 per cycle.

Reoperation for recurrence

Less than 10% of recurrent gliomas recur away from the original tumor

site[64]. Re-operation extends survival by an additional 36 weeks in patients with GBM, and 88 weeks in AA[114, 115] (duration of high quality survival was 10 weeks and 83 weeks respectively, and was lower with pre-op Karnofsky score < 70). In addition to Karnofsky score, significant prognosticators for response to repeat surgery include: age and time from the first operation to re-operation (shorter times → worse prognosis)[109]. Morbidity is higher with reoperation (5-18%); the infection rate is ≈ 3 **x** that for first operation, wound dehiscence is more likely.

OUTCOME

Survival with various grades of astrocytoma

In general, with "optimal treatment" the survival of the various grades of astrocytoma are approximately given in *Table 21-14* (more details may be found in other sections - also *see below* for recursive partitioning analysis (RPA) for GBM).

Low-grade astrocytomas (WHO grade II)

For low grade infiltrating gliomas, *see page 597* for prognosis based on *pre-op* grading.

Table 21-14 Median survival for astrocytomas

Grade	Median survival
I	8-10 yrs
II	7-8 yrs
III	≈ 2-3 yrs
IV	< 1 yr

Malignant astrocytomas (WHO grades III & IV)

The following 3 statistically independent factors affect longevity:

1. patient age: consistently found to be the most significant prognosticator, with younger patients faring better. With GBM, 18 month survival is 50% for patients < 40 yrs, 20% for ages 40-60, and 10% for age > 60116
2. histological features: median survival is 36 mos for AA, and 10 mos for GBM[116] (also, *see below*)
3. performance status (e.g. Karnofsky score **(KPS)** *see page 1182*) at

presentation:

A. with GBM, 18 month survival is 34% for KPS > 70, vs. 13% for KPS < 60116

B. 5-year survival: 7.6% with KPS ≥ 70 pre-op, vs. 3.2% for KPS < 70[6]
With AA, smaller size and frontal location influence survival favorably.

Survival differences between AA and GBM:

Two large studies treated malignant gliomas by surgical resection, 60 Gy whole brain irradiation, and then various chemo-therapy regimens (BCNU, procarbazine, methylprednisolone…) resulted in the survival statistics shown in *Table 21-15*.

Table 21-15 Malignant glioma life table survival statistics[117]

Tumor	– 1-yr survival –		– 2-year survival –	
	Study A	Study B	Study A	Study B
AA	60%	73%	38%	50%
GBM	36%	35%	12%	8%

Recursive partitioning analysis (RPA) with glioblastoma

Analysis of 832 patients with GBM[818] identified 4 risk groups shown in *Table 21-16*.

For example, group 1 (low risk) consists of patient age ≤ 40 years AND who only have tumor located in frontal lobe.

Subgroup analysis found that inclusion of adjuvent chemo-therapy provided minimal increase in survival for patients older than 65 years, for patients > 40 years with KPS < 80, and for those treated with brachytherapy.

Table 21-16 Outcome groups using RPA for GBM

Group	Characteristics	Median survival (wks)	Estimated 2-year survival
1: low risk	• age≤ 40 years • frontal tumor	132	65%
2: low-moderate risk	• age ≤ 40 years • tumor outside frontal lobe	71	35%
3: moderate-high risk	• 40 < age < 65 • KPS > 70 • STR or GTR	63	17%
4: high risk	• age ≥ 65 years • or 40 < age < 65 AND KPS < 80 • or 40 < age < 65 AND KPS ≥ 80 AND biopsy only	37	4%

21.2.2.2. Pilocytic astrocytomas

Key concepts:

- a subgroup of astrocytomas with better prognosis (10-year survival: 94%) than infiltrating fibrillary or diffuse astrocytomas
- age ≤ 20 yrs in 75%, which is lower than for typical astrocytomas
- common locations: cerebellar hemisphere, optic nerve/chiasm, hypothalamus
- radiographic appearance: discrete appearing, contrast enhancing lesion, often cystic with mural nodule
- pathology: compacted and loose textured astrocytes with Rosenthal fibers and/or eosinophilic granular bodies
- danger of overgrading and overtreating if not recognized. Histology alone may be inadequate for diagnosis; knowledge of radiographic appearance is critical

BACKGROUND AND TERMINOLOGY

Pilocytic astrocytoma **(PCA)** is the currently recommended classification of these tumors that have been referred to for many years variously as cystic cerebellar astrocytomas, juvenile pilocytic astrocytomas, optic gliomas, and hypothalamic gliomas[118] (p 77-96). PCAs differ markedly from infiltrating fibrillary or diffuse astrocytomas in terms of their ability to invade tissue and for

malignant degeneration.

Location

PCAs arise throughout the neuraxis and are more common in children and young adults:

1. **optic gliomas** & **hypothalamic gliomas**:
   A. PCAs arising in the optic nerve are called optic gliomas (*see page 606*)
   B. when they occur in the region of the chiasm they cannot always be distinguished clinically or radiographically from so-called hypothalamic gliomas (*see page 606*) or gliomas of the third ventricular region
2. **cerebral hemispheres**: tends to occur in older patients (i.e. young adults) than optic nerve/hypothalamic lesions. These PCAs are potentially confused with fibrillary astrocytomas possessing more malignant potential. PCAs are often distinguished by a cystic component with an enhancing mural nodule (would be atypical for a fibrillary astrocytoma), & some PCAs have dense calcifications[118]
3. **brainstem gliomas**: usually are fibrillary infiltrating type and only a small pro-portion are pilocytic. Those that are PCAs may comprise the majority of the prognostically favorable group described as “dorsally exophytic”[119] (*see page 607*)
4. **cerebellum**: formerly referred to as cystic cerebellar astrocytoma (*see below*)
5. **spinal cord**: PCAs may also occur here, but little information is available on these. Again, patients tend to be younger than with spinal cord fibrillary astrocytomas

Pathology

PCAs are composed of loosely knit tissue comprised of stellate astrocytes in microcystic regions containing eosinophilic granular bodies intermixed with regions of compact tissue consisting of elongated and fibrillated cells often associated with **Rosenthal fiber**[A] formation[118]. These latter two distinctive features facilitate the diagnosis. Another characteristic finding is that the tumors easily break through the pia to fill the over-lying subarachnoid space. PCAs may also infiltrate into the perivascular spaces. Vascular proliferation is common. Multinucleated giant cells with peripherally located nuclei are common,

especially in PCAs of the cerebellum or cerebrum. Mitotic figures may be seen, but are not as ominous as with fibrillary astrocytomas. Areas of necrosis may also be seen. In spite of well-demarcated margins grossly and on MRI, at least 64% of PCAs infiltrate the surrounding parenchyma, especially the white matter[120] (the clinical significance of this is uncertain, one study found no statistically significant decrease in survival[121]).

A. Rosenthal fibers: sausage or corkscrew shaped cytoplasmic eosinophilic inclusion bodies consisting of glial filament aggregates resembling hyaline. Stain bright red on Masson trichrome smears

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Differentiating from a diffuse or infiltrating fibrillary astrocytoma: Unless some of the distinctive findings described above are seen, pathology alone may not be able to differentiate. This may be especially problematic with small specimens obtained e.g. with stereotactic biopsy. Factors that suggest the diagnosis include young age, and knowledge of the radiographic appearance is often critical (*see below*).

Malignant degeneration: Malignant degeneration has been reported, often after many years. This may occur without radiation therapy **(XRT)**[122], although in most cases XRT had been administered[123].

RADIOGRAPHIC APPEARANCE

On CT or MRI, PCAs are usually well circumscribed, 94% enhance with contrast[120] (unlike most low-grade fibrillary astrocytomas), frequently have a cystic component with a mural nodule, and have little or no surrounding edema. Although they may occur anywhere in the CNS, 82% are periventricular[120]. Calcifications are only occasionally present[120]. 4 main imaging patterns of cerebellar or cerebral PCAs are shown in *Table 21-17*.

Table 21-17 Common imaging characteristics of cerebellar or cerebral PCAs

%	Description	
21%	nonenhancing cyst with enhancing mural nodule	} over 66% are cystic with enhancing mural nodule
46%	enhancing cyst with enhancing mural nodule	
16%	mass with nonenhancing central area (necrosis)	
17%	solid mass with minimal or no cyst	

Epidemiology

Usually presents during second decade of life (ages 10-20). 75% occur in age < 20 years[124]. No evidence of gender predilection.

Pilocytic astrocytoma of the cerebellum

Key concepts:

- often cystic, half of these have mural nodule
- usually presents during the second decade of life (ages 10-20 yrs)
- also, see *Key concepts:*, page 603 for pilocytic astrocytomas in general

Formerly referred to by the nonspecific and confusing term **cystic cerebellar astrocytoma**. One of the more common pediatric brain tumors (≈ 10%[125]), comprising 27-40% of pediatric p-fossa tumors[126 (p 367-74), 127 (p 3032)]. They may also occur in adults, where the mean age is lower and the post-operative survival is longer than for fibrillary astrocytomas[128].

Presentation

Signs and symptoms of pilocytic astrocytoma **(PCA)** of the cerebellum are usually those of any p-fossa mass, i.e. those of hydrocephalus or cerebellar dysfunction (see *Posterior fossa (infratentorial) tumors*, page 590).

Pathology

The classic "juvenile pilocytic astrocytoma" of the cerebellum is a distinctive entity with its macroscopic cystic architecture and microscopic spongy appearance[118]. For other microscopic findings, *see above*.

These tumors may be solid, but are more often cystic (hence the older term "cystic cerebellar astrocytoma"), and tend to be large at the time of diagnosis (cystic tumors: 4-5.6 cm dia; solid tumors: 2-4.8 cm dia). Cysts contain highly proteinaceous fluid (averaging ≈ 4 Hounsfield units higher density than CSF on CT[125]).

50% of cystic tumors have a mural nodule and a cyst lining of reactive, non-neoplastic cerebellar tissue or ependymal lining (non-enhancing on CT), whereas the remaining 50% lack a nodule and have a cyst wall of poorly cellular tumor[129] (enhances on CT).

Histological classification of Winston

The Winston classification system[130] is shown in *Table 21-18*. 72% of cerebellar PCAs tended to cluster with either Type A or B characteristics, 18% in his series had both, and 10% had neither.

Table 21-18 Classification of cerebellar astrocytoma

• Type A: microcysts, leptomeningeal deposits, Rosenthal fibers, foci of oligodendroglioma
• Type B: perivascular pseudorosettes, high cell density, mitosis, calcification
• common features of types A & B: hypervascularity, endothelial proliferation, parenchymal desmoplasia, pleomorphism

Treatment guidelines

The natural history of these tumors is slow growth. Treatment of choice is surgical excision of the maximal amount of the tumor that can be removed without producing deficit. In some, invasion of brainstem or involvement of cranial nerves or blood vessels may limit resection. In tumors composed of a nodule with a true cyst, excision of the nodule is sufficient; the cyst wall is non-neoplastic and need not be removed. In tumors with a so-called "false cyst" where the cyst wall is thick and enhances (on CT or MRI), this portion must be removed also. Because of the high 5 and 10 year survival rates together with the high complication rate of radiation therapy over this time interval (see *Radiation injury and necrosis*, page 771) and the fact that many incompletely resected tumors enlarge minimally if at all over periods of 5, 10 or even 20 years, it is recommended to not radiate these patients post-op. Rather, they should be followed with serial CT or MRI and be reoperated if there is recurrence[131]. Radiation therapy is indicated for *nonresectable* recurrence (i.e. reoperation is preferred if possible) or for recurrence with malignant histology. Chemotherapy is preferable to XRT in younger patients[29].

Also, see *Posterior fossa (infratentorial) tumors*, page 590 for guidelines regarding hydrocephalus, etc.

Prognosis

Children with Winston Type A cerebellar PCAs had 94% 10-yr survival, whereas those with Type B had only 29% 10-yr survival.

Tumor recurrence is relatively common, and although it has been said that they generally occur within ≈ 3 yrs of surgery[132], this is controversial and very late recurrences (violating **Collins' law**, which says that a tumor may be considered cured if it does not recur within a time period equal to the patient's age at diagnosis + 9 months) are well known[131]. Also, some tumors excised partially fail to show further growth, representing a form of cure.

About 20% of cases develop hydrocephalus requiring treatment following surgery[133]. So-called "drop metastases" are rare with PCAs.

OPTIC GLIOMA

Accounts for ≈ 2% of gliomas in adults, and 7% in children. The incidence is higher (≈ 25%) in neurofibromatosis **(NFT)** (*see page 722*).

May arise in any of the following patterns:

1. one optic nerve (without chiasmal involvement)
2. optic chiasm: less commonly involved in patients with NFT than in sporadic cases
3. multicentric in both optic nerves sparing the chiasm: almost only seen in NFT
4. may occur in conjunction with or be part of a hypothalamic glioma (*see below*)

Pathology

Most are composed of low-grade (pilocytic) astrocytes. Rarely malignant.

Presentation

Painless proptosis is an early sign in lesions involving one optic nerve. Chiasmal lesions produce variable and nonspecific visual defects (usually monocular) without proptosis. Large chiasmal tumors may cause hypothalamic and pituitary dysfunction, and may produce hydrocephalus by obstruction at the foramen of Monro. Gliosis of the optic nerve head may be seen on fundoscopy.

Evaluation

Plain x-rays: not usually helpful, although in some cases dilatation of the optic canal can be seen in optic canal views.

CT/MRI: CT scan is excellent for imaging structures within the orbit. MRI is helpful for demonstrating chiasmal or hypothalamic involvement. On CT or MRI, involvement of the optic nerve produces contrast enhancing fusiform enlargement of the nerve usually extending > 1 cm in length.

Treatment

Tumor involving a single optic nerve, sparing the chiasm, producing

proptosis and visual loss should be treated with a transcranial approach with excision of the nerve from the globe all the way back to the chiasm (a transorbital (Kronlein) approach is not appropriate since tumor may be left in the nerve stump). In addition to the anticipated blindness in the involved eye, this may produce a junctional scotoma (*see page 1071*).

Chiasmal tumors are generally not treated surgically except for biopsy (especially when it is difficult to distinguish an optic nerve glioma from a hypothalamic glioma), CSF shunting, or to remove the rare exophytic component to try and improve vision.

Further treatment: Chemotherapy[29] (especially in younger patients) or XRT is used for chiasmal tumors, for multicentric tumors, post-op if tumor is found in the chiasmal stump end of the resected nerve, and for the rare malignant tumor. Typical XRT treatment planning is for 45 Gy given in 25 fractions of 1.8 Gy.

HYPOTHALAMIC GLIOMA

Pilocytic astrocytomas of the hypothalamus and third ventricular region occur primarily in children. Radiographically, the lesion may have an intraventricular appearance. Many of these tumors have some chiasmal involvement and the distinction from optic nerve glioma cannot be made (*see above*).

May present with so-called "**diencephalic syndrome**", a rare syndrome seen in peds, usually caused by an infiltrating glioma of the anterior hypothalamus. Classically: cachexia (loss of subcutaneous fat) associated with hyperactivity, over-alertness and an almost euphoric affect. May also see: hypoglycemia, failure to thrive, macrocephaly.

When complete resection is not possible, further treatment may be needed as outlined under optic gliomas (see *Astrocytoma* above).

PILOMYXOID ASTROCYTOMA (PMA)

WHO grade II. Related to pilocytic astrocytomas **(PCA)** but more aggressive with greater tendency to recur and spread in CSF[134]. May be an infantile form of PCA with a case report of "maturation" to a typical PCA[135]. Typical onset in infancy (10 months).

Histologically: dominant mucoid matrix, monomorphic bipolar cells, and angiocentric cell arrangement. By definition, does not contain Rosenthal fibers.

May also occur in spinal cord, with a case report of extraneural peritoneal mets spread through a VP shunt[136].

21.2.2.3. Brainstem glioma

Key concepts:

> - not a homogeneous group. MRI can differentiate malignant from benign lesions
> - trend: lower grade tumors tend to occur in the upper brainstem, and higher grade tumors in the lower brainstem/medulla
> - usually presents with multiple cranial nerve palsies and long tract findings
> - most are malignant, have poor prognosis, and are not surgical candidates
> - role of surgery primarily limited to dorsally exophytic lesions and shunting

Brainstem gliomas **(BSG)** tend to occur during childhood and adolescence (77% are < 20 yrs old, they comprise 1% of adult tumors[137]). BSG are one of the 3 most common brain tumors in pediatrics (see *Pediatric brain tumors*, page 697), comprising ≈ 10-20% of pediatric CNS tumors[119].

PRESENTATION[138]

Upper brainstem tumors tend to present with cerebellar findings and hydrocephalus, whereas lower brainstem tumors tend to present with multiple lower cranial nerve deficits and long tract findings. Due to their invasive nature, signs and symptoms usually do not occur until the tumor is fairly extensive in size.

Signs and symptoms:

1. gait disturbance
2. headache (*see page 587*)
3. nausea/vomiting
4. cranial nerve deficits: diplopia, facial asymmetry
5. distal motor weakness in 30%
6. papilledema in 50%
7. hydrocephalus in 60%, usually due to aqueductal obstruction (often late, except with periaqueductal tumors, e.g. see *Tectal gliomas* below)
8. failure to thrive (especially in age ≤ 2 yrs)

PATHOLOGY

BSG is a heterogeneous group. There may be a tendency towards lower grade tumors in the upper brainstem (76% were low-grade) versus the lower

brainstem (100% of the glioblastomas were in the medulla)[139]. A cystic component is seen rarely. Calcifications are also rare. 4 growth patterns that can be identified by MRI[140] that may correlate with prognosis[141]:

1. **diffuse**: all are malignant (most are anaplastic astrocytomas, the rest are glioblastomas). On MRI these tumors extend into the adjacent region in vertical axis (e.g. medullary tumors extend into pons and/or cervical cord) with very little growth towards obex, remaining intraaxial
2. **cervicomedullary**: most (72%) are low-grade astrocytomas. The rostral extent of these tumors is limited to the spinomedullary junction. Most bulge into the obex of the 4th ventricle (some may have an actual exophytic component)
3. **focal**: extent limited to medulla (does not extend up into pons nor down into spinal cord). Most (66%) are low-grade astrocytomas
4. dorsally exophytic: may be an extension of “focal” tumors (*see above*). Many of these may actually be low grade gliomas including:
   A. pilocytic astrocytomas: *see page 603*
   B. **gangliogliomas** (*see page 677*): very rare, only 13 cases reported as of 1984. Compared to other BSGs, these patients tend to be slightly older and the medulla is involved more frequently[142]

EVALUATION

MRI

The diagnostic test of choice. MRI evaluates status of ventricles, gives optimal assessment of tumor (CT is poor in the posterior fossa) and detects exophytic component. T1WI: almost all are hypointense, homogeneous (excluding cysts). T2WI: increased signal, homogeneous (excluding cysts). Gadolinium enhancement is highly variable[140].

CT

Most do not enhance on CT, except possibly an exophytic component. If there is marked enhancement, consider other diagnoses (e.g. high grade vermian astrocytoma).

TREATMENT

Surgery

Biopsy: should not be performed when the MRI shows a diffuse infiltrating brainstem lesion[143] (does not change treatment or outcome).

Treatment is usually non-surgical. Exceptions where surgery may be indicated:

1. tumors with a dorsally exophytic component[119]: *see below* these may protrude into 4th ventricle or CP angle, tend to enhance with IV contrast, tend to be lower grade
2. some success has been achieved with non-exophytic tumors that are not malignant astrocytomas (surgery in malignant astrocytomas is without benefit)[141] (detailed follow-up is lacking)
3. shunting for hydrocephalus

Dorsally exophytic tumors

These tumors are generally histologically benign (e.g. gangliogliomas) and are amenable to radical subtotal resection. Prolonged survival is possible, with a low incidence of disease progression at short-term follow-up[119].

Surgical goals in exophytic tumors include:

1. enhanced survival by subtotal removal of exophytic component[144]: broad attachment to the floor of 4th ventricle is typical and usually precludes complete excision (although some "safe entry" zones have been described[145]). An ultrasonic aspirator facilitates debulking
2. establishing diagnosis: radiographic differentiation of exophytic brainstem gliomas tumors from other lesions (e.g. medulloblastoma, ependymoma and dermoids) may be difficult
3. tumors that demonstrate recurrent growth after resection remained histologically benign and were amenable to re-resection[119]

Complications of surgery generally consisted of exacerbation of pre-operative symptoms (ataxia, cranial nerve palsies…) which usually resolved with time.

Medical

No proven chemotherapeutic regimen. Steroids are usually administered. In pediatrics, there is some indication of response to Temodar® (temozolomide, *see page 602*).

RADIATION

Traditionally given as 45-55 Gy over a six week period, five days per week. When combined with steroids, symptomatic improvement occurs in 80% of patients.

Possible improved survival with so called "**hyperfractionation**" where multiple smaller doses per day are used.

PROGNOSIS

Most children with malignant BSG will die within 6-12 months of diagnosis. XRT may not prolong survival in patients with grade III or IV tumors. A subgroup of children have a more slowly growing tumor and may have up to 50% five-year survival. Dorsally exophytic tumors comprised of pilocytic astrocytomas may have a better prognosis.

TECTAL GLIOMAS

A topically defined diagnosis generally consisting of low-grade astrocytomas. Considered a benign subgroup of brainstem glioma. Because of location, tends to present with hydrocephalus. Focal neurologic findings are rare (diplopia, visual field deficits, nystagmus, Parinaud's syndrome (*see page 114*), ataxia, seizures…) and are often reversible after the hydrocephalus is corrected.

Epidemiology

Comprises ≈ 6% of *surgically* treated pediatric brain tumors[146]. Presents primarily in childhood. Median age of patients becoming symptomatic = 6-14 years[146].

Pathology

Since many of these are not biopsied, meaningful statistical analysis is not possible. Pathologies identified include: WHO II diffuse astrocytoma, pilocytic astrocytomas, WHO II ependymoma, anaplastic astrocytoma, oligodendroglioma & oligoastrocytoma.

Radiographic evaluation

CT scan detects the hydrocephalus, but may miss the tumor in ≈ 50%[147]. Calcification on CT has been described in 9-25%[147, 148].

MRI is the study of choice for diagnosis and follow-up. Typically appears as a mass projecting dorsally from the quadrigeminal plate. Isointense on T1WI, iso- or hyperintense on T2WI[146, 149]. Enhancement with gadolinium occurs in 18% and is of uncertain prognostic significance.

Treatment

Due to the indolent course, open surgery is not recommended. Options include:

1. VP shunt: the standard treatment for years. Long-term results are good with a functioning shunt
2. endoscopic third ventriculostomy: may avoid the need for a shunt. Endoscopic biopsy[150] may be done at the same time through the same burr hole if it is technically feasible (requires a dilated foramen of Monro, which is often present). Long-term results unknown
3. endoscopic aqueductoplasty (with or without stenting): an option for some. Long-term results unknown

Stereotactic radiosurgery: May be offered for tumor progression (criteria are not defined: radiographic progression may not be associated with clinical deterioration[149]). Dosing should be limited to ≤ 14 Gray at the 50-70% isodose line to avoid radiation-induced side effects[151].

Prognosis

Tumor progression: described in 15-25%.

Follow-up: no accepted guidelines. Serial neurologic exams and MRIs every 6-12 months has been suggested[146].

21.2.3. Oligodendroglioma

Key concepts:

- frequently presents with seizures
- predilection for the frontal lobes
- histology: classic features of “fried egg” cytoplasm (on permanent pathology) & “chicken wire” vasculature are unreliable. Calcifications are common
- grading: controversial. Recommendation: low grade and high grade
- recommended treatment: surgery for mass effect or low grade lesions (high-

grade lesions are controversial). Chemotherapy for all (with or without surgery), XRT only for anaplastic transformation

Table 21-19 Location of oligodendrogliomas

Location	%
supratentorial	> 90%
frontal lobes	45%
hemisphere (outside frontal lobes)	40%
within third or lateral ventricle	15%
infratentorial + spinal cord	< 10%

EPIDEMIOLOGY

Oligodendroglioma **(ODG)** have long been thought to comprise only ≈ 2-4% of primary brain tumors[152, 153] or 4-8% of cerebral gliomas[153]; but recent evidence indicates these tumors have been underdiagnosed (many are misinterpreted as fibrillary astrocytomas, especially the infiltrative portion of these tumors) and ODGs may represent up to 25-33% of *glial* tumors[154, 155]. Ratio of male:female = 3:2. Primarily a tumor of adults: average age ≈ 40 years (peak between 26-46 years), but with a smaller earlier peak in childhood between 6-12 years[156]. CSF metastases reportedly occur in up to 10%, but 1% may be a more realistic estimate[152]. Spinal ODGs comprise only ≈ 2.6% of intramedullary tumors of the cord and filum.

CLINICAL

Classic presentation of ODG: a patient with seizures for many years prior to the diagnosis being made when they would present with an apoplectic event due to peri-tumoral intracerebral hemorrhage. This scenario is less common in the post CT era.

Seizures are the presenting symptoms in ≈ 50-80% of cases[152, 156]. The remainder of presenting symptoms are non-specific for ODG, and are more often related to local mass effect and less commonly to ↑ ICP. Presenting symptoms are shown in *Table 21-20*.

Table 21-20 Presenting symptoms in 208 oligodendrogliomas[152]

Symptom	%
seizures	57%

headache	22%
mental status changes	10%
vertigo/nausea	9%

EVALUATION

Calcifications are seen in 28-60% of ODGs on plain radiographs[152], and on 90% of CTs.

PATHOLOGY

73% of tumors have microscopic calcifications[157]. Isolated tumor cells consistently penetrate largely intact parenchyma, an associated solid tumor component may or may not be present[155]. The solid portion, when present, classically demonstrates lucent peri-nuclear halos giving a "fried egg" appearance (actually an artifact of formalin fixation, which is not present on frozen section and may make diagnosis difficult on frozen). A "chicken-wire" vascular pattern has also been described[158]. These features are felt to be unreliable, and cells with monotonous round nuclei (often in cellular sheets) with an eccentric rim of eosinophilic cytoplasm lacking obvious cell processes are more consistent features[159].

16% of hemispheric ODGs are cystic[157] (cysts form from coalescence of microcysts from micro-hemorrhages, unlike astrocytomas which actively secrete fluid).

33-41% have a component of ependymal or neoplastic astrocytic cells (so called oligoastrocytomas or **mixed gliomas**[160] or **collision tumors**) (*see page 612*).

GFAP staining: Since most ODGs contain microtubules instead of glial filaments[161], ODGs usually do not stain for GFAP (*see page 720*) although some do[162]. In mixed gliomas, the astrocytic component may stain for GFAP.

GRADING

A work-in-progress. Historically, a number of attempts at grading ODGs have been proposed and then abandoned because of lack of prognostic significance (for a review, see reference[159]). Necrosis does not appear to reliably predict a poor prognosis[159].

For prognostic purposes, it is suggested that ODGs be stratified into two groups:

• oligodendroglioma (WHO grade II) or low grade

• anaplastic oligodendroglioma (WHO grade III) or high grade[153, 159]

Although there is not uniform agreement on the means for differentiating the two, the factors shown in *Table 21-21* should be taken into account as they have been demonstrated to have prognostic significance. Using the spatial grading system for low grade gliomas (*see page 591*), no ODGs are of the Type 1 tumor (solid tumor without infiltrative component).

Table 21-21 Features associated with low-grade and high-grade oligodendrogliomas

Feature	WHO II (low grade)	WHO III (high grade)
contrast enhancement on CT or MRI	absent	present
endothelial proliferation on histology	absent	present
pleomorphism (large variability in nuclear and cytoplasmic size and shape)	absent	present
tumor proliferation (evidenced by mitotic figures or high MIB-1 index*)	absent	present
astrocytic component	absent	present

* see page 720 for information on the MIB-1 index

TREATMENT

> Σ **Recommendation:** (*see text for details*). Following an appropriate surgical procedure (if indicated), chemotherapy is the primary treatment modality. XRT is reserved for anaplastic transformation, if it should occur[159]

CHEMOTHERAPY

Most ODGs respond to chemotherapy, usually in < 3 mos, often with a reduction in size. The response is variable in degree and duration[163]. No pathological or clinical feature of high-grade ODGs has been identified that reliably predicts response to chemo-therapy. However, allelic loss of chromosome 1p, and combined loss of chromosome arms 1p and 19q, are associated with response to chemo; and losses of both 1p and 19q were associated with longer tumor-free survival after chemo[164].

The most experience is with PCV (procarbazine 60 mg/m^2 IV, CCNU AKA lomustine (CeeNU®) 110 mg/m^2 PO, and vincristine 1.4 mg/m^2 IV, all given on a 29 day cycle repeated every 6 weeks)[165, 166]. Also studied: temozolomide for

recurrent anaplastic oligoastrocytoma showed some efficacy[112].

SURGERY

Indications for surgery:

1. ODGs with significant mass effect regardless of grade: surgery decreases the need for corticosteroids, reduces symptoms and prolongs survival[159]
2. tumors without significant mass effect:
    A. <u>low-grade</u> ODGs and oligoastrocytoma: surgery is recommended for resectable lesions. Gross total removal should be attempted when possible (survival is improved even more than with astrocytomas[167]), but not at the expense of neurologic function
    B. <u>high-grade</u> ODGs: data for improved survival is less convincing, and some studies show no advantage of gross total removal over partially resected or biopsied-only high-grade lesions[159]

Grossly, the tumor appears as a pink to red, friable mass. There may be a false plane of demarcation between tumor and what appears to be normal brain.

POSTOPERATIVE RADIATION

Benefits of postoperative irradiation is controversial[156]. In a retrospective analysis with no set selection criteria, survival was better in patients receiving > 45 Gy (1 Gy = 100 cGy)[168]. In another series, no difference in 5 year survival following surgery was seen with or without XRT (amount of radiation not specified)[169]. Radiation side effects of memory loss, dementia and personality changes are more common with the longer survival seen in many of these cases[170].

PROGNOSIS

Pure ODGs have a better prognosis than mixed oligoastrocytomas which are better than pure astrocytomas (an oligodendroglial component, no matter how small, confers a better prognosis).

10 year survival of 10-30% has been quoted for tumors that are completely or predominantly ODGs[168]. As a group, median survival for surgically treated lesions is given as 35 months post-op (mean 52 months)[152].

The presence of calcifications is debated as a prognosticator; in one series, calcified ODG on plain films had a longer median survival of 108 months (vs. 58 months for noncalcified)[152].

Frontal lobe ODGs survived longer than those in temporal lobes (37 months vs. 28 months postoperative survival)[152], possibly due to increased ease of radical resection with the former.

Chromosomal 1p loss (or combined 1p and 19q loss) is also associated with longer survival[164, 171].

21.2.4. Mixed gliomas

21.2.4.1. Oligoastrocytoma

Molecular biology: May show changes typical for diffuse astrocytoma (*TP*[53] mutation & LOH on 17p) or for ODG (LOH on 1p and 19q). No molecular genetic markers have been identified to distinguish oligoastrocytoma from either astrocytoma or ODG. Unlike ODG, the prognostic/therapeutic value of LOH on 1p is less clear[171].

Oligoastrocytoma (WHO grade II)

Two distinct neoplastic cell types, 1 type resembles oligodendroglioma cells, and the other resembles cells in diffuse astrocytomas. Some cells may have features of both. The 2 cell types may be segregated or diffusely admixed.

Anaplastic oligoastrocytoma (WHO grade III)

Increased cellularity, nuclear atypia, pleomorphism, and high mitotic activity. Necrosis and microvascular proliferation may be present. Differentiating from GBM may be difficult since GMS may have areas resembling anaplastic ODG (the term "glioblastoma with oligodendroglioma component" is a disputed term suggested for these - unproven suggestion that survival may be better than for ordinary GBM[172]).

21.2.5. Neuronal and mixed neuronal-glial tumors

21.2.5.1. Desmoplastic infantile astrocytoma/ganglioglioma

The former entities "desmoplastic cerebral astrocytoma of infancy" and "desmoplastic infantile ganglioglioma" have been combined to "desmoplastic

infantile astrocytoma and ganglioglioma" **(DIG)**[5]. A lesion with either astrocytic or dual glio-neuronal differentiation. Prognosis is usually favorable.

21.2.5.2. Central neurocytoma

Rare. Usually considered benign, but malignant variation/behavior has been described[173]. Slow-growing well circumscribed tumor usually located in the lateral ventricles or at the septum pellucidum[174, 175]. Tends to affect young adults, usually males. Histologically, resembles oligodendrogliomas. Ultrastructure shows neuronal differentiation. Molecular oncogenesis is not known.

Usually curable by total resection[175]. Subtotal resection and histologic atypia are associated with an increased risk of recurrence, but early recurrence may occur even without malignant histologic features[173].

Variants:

1. "extraventricular neurocytomas": neurocytic neoplasms located within brain parenchyma. Not as well characterized as intraventricular type[175]
2. central liponeurocytoma: extremely rare. Classified as a glioneuronal tumor. Usually occurs in the posterior fossa of older adults[176]. Once considered a variant of medulloblastoma (called medullocytoma), has more indolent behavior[177] and characteristic morphologic features of well-differentiated neurons with the cytology of neurocytes in addition to a population of lipidized cells resembling mature adipose tissue[177]

Treatment

1. ideal: total resection if possible
2. stereotactic radiosurgery may be effective for recurrence[178] or for incompletely removed or biopsied tumors[179]
3. chemotherapy with etoposide, cisplatin and cyclophosphamide, has been reported for recurrent progressive tumor[180]

21.2.5.3. Cerebellar liponeurocytoma

Née lipomatous medulloblastoma. Occurs exclusively in cerebellum of adults (mean age: 50 years). No gender preference.

Histology: clusters of neoplastic neurocytes with lipidization (resembling

adipocytes) with background of small neoplastic cells with morphological features more suggestive of neurocytes. Synaptophysin (*see page 721*) and MAP-2 immunostaining is consistent and diffuse, focal GFAP staining is common. Usually no mitotic figures. MIB-1 index 1-3%.

21.2.6. Meningiomas

Key concepts:

> - slow growing, extra-axial tumor, usually benign, arise from arachnoid (not dura)
> - imaging (MRI or CT): classically broad based attachment on dura often with dural tail, typically enhance densely, may cause hyperostosis of adjacent bone
> - MRI: isointense on T1WI, hypodense on T2WI
> - 32% of incidentally discovered meningiomas do not grow over 3 years follow-up
> - surgical indications: documented growth on serial imaging and/or symptoms referable to the lesion that are not satisfactorily controlled medically
> - most (but not all) are cured if completely removed, which is not always possible
> - most commonly located along falx, convexity, or sphenoid bone
> - frequently calcified. Classic histological finding: psammoma bodies

Usually slow growing, circumscribed (non-infiltrating), benign lesions. Histologically malignant (incidence: ≈ 1.7% of meningiomas[181]) and/or rapidly growing varieties are also described (a rapidly growing lesion that looks like a meningioma may be a hemangiopericytoma, *see page 620*). Actually arise from arachnoid cap cells (not dura). May be multiple in up to 8% of cases[182], this finding is more common in neurofibromatosis. Occasionally forms a diffuse sheet of tumor (**meningioma en plaque**). This section considers intracranial meningiomas.

May occur anywhere that arachnoid cells are found (between brain and skull, within ventricles, and along spinal cord). Ectopic meningiomas may arise within the bone of the skull (**primary intraosseous meningiomas**)[183] and others occur in the subcutaneous tissue with no attachment to the skull. Most are asymptomatic (*see below*).

EPIDEMIOLOGY

As many as 3% of autopsies on patients > 60 yrs age reveals a meningioma[184]. Meningiomas account for 14.3-19% of primary intracranial neoplasms[185]. Incidence peaks at 45 years age. Female:male ratio is 1.8:1.

1.5% occur in childhood and adolescence, usually between 10-20 years age[127 (p 3263)]. 19-24% of adolescent meningiomas occur in patients with neurofibromatosis type I.

LOCATION

Table 21-22 lists common locations. Other locations include: CP-angle, clivus, planum sphenoidale and foramen magnum. ≈ 60-70% occur along the falx (including parasagittal), along sphenoid bone (including tuberculum sellae), or over the convexity. Childhood meningiomas are rare, 28% are intraventricular, and the posterior fossa is also a common site.

Table 21-22 Location of adult meningiomas (series of 336 cases[186])

Location	%
parasagittal	20.8
convexity	15.2
tuberculum sellae	12.8
sphenoidal ridge	11.9
olfactory groove	9.8
falx	8
lateral ventricle	4.2
tentorial	3.6
middle fossa	3
orbital	1.2
spinal	1.2
intrasylvian	0.3
extracalvarial	0.3
multiple	0.9

Sphenoid wing (or ridge) meningiomas

Three basic categories[187]:

1. lateral sphenoid wing (or pterional): behavior and treatment are usually similar to convexity meningioma
2. middle third (or alar)
3. medial (clinoidal): tend to encase the ICA and the MCA as well as cranial nerves in the region of the superior orbital fissure and the optic nerve. May compress brainstem. Total removal is often not possible

Parasagittal and falx meningiomas

Up to 50% invade the superior sagittal sinus **(SSS)**. Grouped based on location along AP direction of SSS as:

1. anterior (ethmoidal plate to coronal suture): 33%. Most often present with H/A and mental status changes
2. middle (between coronal and lambdoidal sutures): 50%. Most often present as Jacksonian seizure and progressive monoplegia
3. posterior (lambdoidal suture to torcular Herophili): 20%. Most often present with H/A, visual symptoms, focal seizures, or mental status changes

Classification systems for the extent of SSS invasion include one by Bonnal and Brotchi[188], and a more recent one by Sindou et al.[189] shown in *Figure 21-1*.

Parasagittal meningiomas may originate at the level of the motor strip, and a common initial manifestation of these is a contralateral foot drop[190].

Olfactory groove meningiomas

Presentation (usually asymptomatic until they are large) may include:

1. Foster Kennedy syndrome: anosmia (patient is usually unaware of this), ipsilateral optic atrophy, contralateral papilledema (*see page 112*)
2. mental status changes: often with frontal lobe findings (apathy, abulia…)
3. urinary incontinence
4. posteriorly located lesions may compress the optic apparatus causing visual impairment
5. large lesions may compress the fornix and cause short-term memory loss
6. seizure

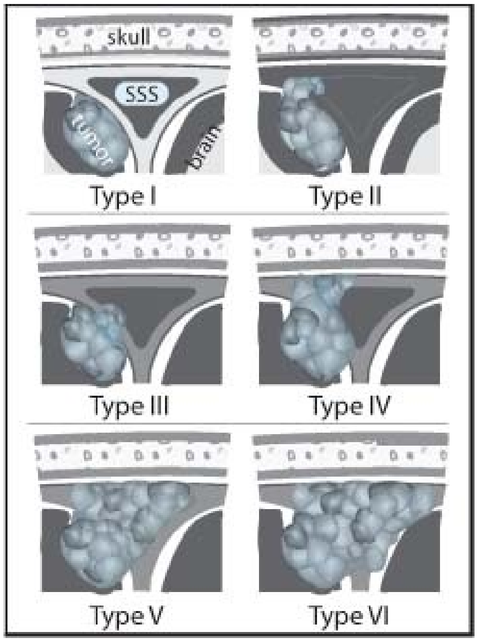

Figure 21-1 Grading system for meningioma invasion of the superior sagittal sinus Modified from Sindou MP et al., **J Neurosurg**, 105: pp 514-25, 2006 Shown: schematic coronal section through superior sagittal sinus **(SSS)**. Type I = attachment to lateral wall of sinus; Type II = invasion of lateral recess; Type III = invasion of lateral wall; Type IV = invasion of lateral wall and roof; Type V = total sinus occlusion, contralateral wall spared; Type VI = total sinus occlusion, invasion of all walls

The morbidity, mortality and difficulty in achieving total removal increase significantly for tumors > 3 cm in size[191].

Pre-op MRA, CTA or angiogram may be helpful to assess location of anterior cerebral arteries relative to the tumor. 70-80% of these get the majority of their blood supply from the anterior ethmoidal artery, which is usually not embolized due to risk to ophthalmic artery (and blindness). If there are substantial middle meningeal feeders, these may be embolized, but the benefit tends to be small.

Planum spehnoidale meningiomas

Arise from the flat part of the sphenoid bone anterior to the chiasmatic sulcus in the posterior part of the anterior cranial fossa.

Tuberculum sellae meningiomas (TSM)

The site of origin of these tumors is only about 2 cm posterior to that of olfactory groove meningiomas[191]. The **tuberculum sellae** is the bony elevation between the chiasmatic sulcus and the sella turcica. By definition, the anterior margin of the chiasmatic sulcus (the limbus sphenoidale) is the demarcation

between the anterior and middle cranial fossa. Therefore these tumors originate in the middle fossa (unlike planum sphenoi-dale meningiomas which are in the anterior fossa).

TSMs are notorious for producing visual loss (chiasmal syndrome = primary optic atrophy + bitemporal hemianopsia). When a TSM grows posteriorly into the sella turcica it may be mistaken for a pituitary macroadenoma (*see page 1216* for MRI and differentiating features).

Foramen magnum meningiomas

As with any foramen magnum **(FM)** lesion, the neurologic symptoms and signs can be very confusing and often do not initially suggest a tumor in this location (*see page 711*).

In the French Cooperative Study, there were 106 FM meningiomas[192], 31% arose from the anterior lip, 56% were lateral, and 13% arose from the posterior lip of the FM. Most are intradural, but they can be extradural or a combination (the latter 2 have a lateral origin and are often invasive, which makes total removal more difficult)[193]. They may be above, below, or on both sides of the vertebral artery[193].

ASYMPTOMATIC MENINGIOMAS

Meningiomas are the most common *primary* intracranial tumors, and most remain asymptomatic throughout the patient's life[194]. The routine use of CT & MRI for numerous indications inevitably results in the discovery of incidental (asymptomatic) meningiomas. In a population[A] based study[194], incidental meningiomas were seen in 0.9% of MRIs. In another series, 32% of primary brain tumors seen on imaging studies were meningiomas, and 39% of these were asymptomatic[195]. Of 63 cases followed for > 1 year with non-surgical management, 68% showed no increase in size over an average follow-up of 36.6 mos, whereas 32% increased in size over 28 mos average follow-up[195]. Asymptomatic meningiomas with calcification seen on CT and/or hypointensity on T2WI MRI appeared to have a slower growth rate[195].

A. the study population was middle class caucasians and result may not be generalized to other groups

Data is lacking to make evidence-based management guidelines. A

suggestion is to obtain a follow-up imaging study 3-4 months after the initial study to rule-out rapid progression, and then repeat annually for 2-3 years. The development of symptoms would prompt performing a study at that time.

Treatment is indicated for lesions that produce symptoms that cannot be satisfactorily controlled medically, or for those that demonstrate significant continued growth on serial imaging studies. When surgery was performed, the perioperative morbidity rate was statistically significantly higher in patients > 70 years old (23%) than in those < 70 (3.5%)[195].

PATHOLOGY

Four critical histopathological variables:

1. grade } *see Table 21-23*
2. histological subtype } *see Table 21-23*
3. proliferation indices: *see page 616*
4. brain invasion: *see page 616*

Table 21-23 WHO classification of meningiomas

WHO Grade I	meningothelial fibrous (fibroblastic) transitional (mixed) psammomatous angiomatous microcystic secretory lymphoplasmacyte-rich metaplastic
WHO II	chordoid clear cell (intracranial) atypical
WHO III	papillary rhabdoid (*see text*) anaplastic

There are a number of pathologic classification systems[3, 196, 197 (p 465)], and transitional forms between the major types exist. More than one histological pattern may be seen in a given tumor. The WHO 2000 classification is shown in *Table 21-23*.

1. meningiomas with low recurrence risk and/or aggressive growth (WHO grade I)

A. **meningothelial** or **meningotheliomatous**, AKA **syncytial**: the most common. Sheets of polygonal cells. Some use the term **angiomatous** for meningotheliomatous variety with closely packed blood vessels
B. **fibrous** or **fibroblastic**: cells separated by connective tissue stroma. Consistency is more rubbery than meningotheliomatous or transitional
C. **transitional**: intermediate between meningotheliomatous and fibrous. Cells tend to be spindle shaped, but areas of typical meningotheliomatous cells occur. Whorls, some of which are calcified (psammoma bodies)
D. psammomatous: calcified meningothelial whorls
E. angiomatous
F. **microcystic**: AKA "humid" or vacuolated meningioma. The characteristic dilated extracellular spaces are usually empty, but occasionally contain substance that stains positive for PAS (? glycoprotein) or contain fat[198]. The cysts may coalesce and form grossly or radiologically visible cysts and may resemble astrocytomas
G. secretory
H. lymphoplasmacyte-rich

2. meningiomas with greater recurrence risk and/or aggressive growth include
   A. **atypical meningioma**: increased mitotic activity (1-2 mitotic figure/high-powered field), increased cellularity, focal areas of necrosis, giant cells. Cellular pleomorphism is not unusual but is not significant in and of itself. Increasing atypia appears to correlate with increasing aggressiveness
   B. **rhabdoid meningiomas**: usually have malignant features and behave aggressively. Behavior in the absence of malignant features is undetermined[2]
   C. **malignant meningiomas**: AKA anaplastic, papillary or sarcomatous. Characterized by frequent mitotic figures, cortical invasion, rapid recurrence even after apparent total removal[199], and, rarely, metastases (*see below*). Frequent mitotic figures (≥ 4 mitoses per high-power field) or the presence of papillary features are strong predictors of malignancy. May be more common in younger patients

Obsolete terms (in the current WHO classification) presented for context in older literature: metaplastic, myxomatous, xanthomatous (abundant cytoplasmic lipids; appear vacuolated), lipomatous, granular, chondroblastic, osteoblastic,

melanotic. Angioblastic or (meningeal) hemangiopericytomas (true hemangiopericytomas are sarcomas, *see page 620*). (others use the term "angioblastic" for tumors histologically similar to hemangioblastoma. Angioblastic meningiomas were felt to have more malignant clinical characteristics than other forms[197 (p 479-83)].

Proliferation indices

Due to variation between institutions and observers, it is advised that proliferation indices (e.g. Ki-67 or MIB-1) not be used as the sole discriminant for grading. However, these indices do correlate with prognosis (*see Table 21-24*). Adding the phrase "with high proliferative activity" is suggested for tumors with a very high index[2].

Brain invasion

The presence of brain invasion increases the likelihood of recurrence to levels similar to atypical meningiomas (not anaplastic)[201], but is not an indicator of malignant grade. Brain invasion in atypical meningiomas does not dictate malignant behavior. Adding the phrase "with brain invasion" is suggested to denote higher risk of recurrence[2].

Table 21-24 Ki-67 proliferation index in meningiomas[200]*

Description & WHO grade	Mean Ki-67 index*	Recurrence rate
Common meningioma (WHO grade I)	0.7%	9%
Atypical meningioma (WHO grade II)	2.1%	29%
Anaplastic meningioma (WHO grade III)	11%	50%

* not recommended for grading (*see text*)

Metastases

Very rarely a meningioma may metastasize outside the CNS. Most of these are angioblastic or malignant. Lung, liver, lymph nodes and heart are the most common sites.

DIFFERENTIAL DIAGNOSIS/DIAGNOSTIC CONSIDERATIONS OF MENINGIOMA

1. multiple meningiomas: suggests neurofibromatosis 2 (NF2)
2. pleomorphic xanthastrocytoma (PXA): may mimic meningiomas since they tend to be peripherally located and may have a dural tail (*see* *page 592*)
3. **Rosai-Dorfman disease**: especially if extracranial lesions are also identified. A connective tissue disorder with sinus histiocytosis and massive painless lymphadenopathy (most have cervical lymphadenopathy). Usually in young adults. Isolated intracranial involvement is rare. MRI: dural-based enhancing mass with signal characteristics similar to meningioma, may have dural tail. Most common intracranial locations: cerebral convexities, parasagittal, suprasellar, cavernous sinus. Pathology: dense fibrocollagenous connective tissue with spindle cells and lymphocytic infiltration, stains for CD68 & S-100. Histiocytic proliferation without malignancy. Foamy histiocytes are characteristic. Surgery and immunosuppressive therapy not effective. Low-dose XRT may be the best option

EVALUATION

MRI

Occasionally may be isointense with brain on T1WI and T2WI, but most enhance with gadolinium. Brain edema may or may not be present. Calcifications appear as signal voids on MRI. Gives information regarding patency of dural venous sinuses (accuracy in predicting sinus involvement is ≈ 90%[202]). “Dural tail” is a common finding[203].

CT

Homogeneous, densely enhancing mass with broad base of attachment along dural border. Non-contrast Hounsfield numbers of 60-70 in a meningioma usually correlates with presence of psammomatous calcifications. There may be little cerebral edema, or it may be marked and may extend throughout the white matter of the entire hemisphere.

Intraventricular meningiomas: 50% produce extraventricular edema. On angio, these may falsely appear malignant.

Prostate cancer may mimic meningioma (prostate mets to brain are rare, but prostate frequently goes to bone, and may go to skull and can cause hyperostosis).

Angiography

Classic pattern: “comes early, stays late” (appears early in arterial phase, blush persists beyond venous phase). Meningiomas characteristically have external carotid artery feeders. Exceptions: low frontal median (e.g. olfactory groove) meningiomas which feed from the ICA (ethmoidal branches of the ophthalmic artery). Suprasellar meningiomas may also be fed by large branches of the ophthalmic arteries. Parasellar meningiomas tend to feed from the ICA. Secondary vascular supply may be derived from pial branches of the anterior, middle, and posterior cerebral arteries.

Artery of **Bernasconi & Cassinari** AKA artery of tentorium (a branch of the meningohypophyseal trunk) AKA the “Italian” artery: enlarged in lesions involving tentorium (e.g. tentorial meningiomas).

Angiography also gives information about occlusion of dural venous sinuses, especially for parasagittal/falx meningiomas. Oblique views are often best for evaluating patency of the superior sagittal sinus **(SSS)**. Angiography can also help confirm diagnosis by the distinctive prolonged homogeneous tumor blush. Angiography also provides an opportunity for pre-op embolization (*see below*).

Pre-op embolization: Reduces the vascularity of these often bloody tumors, facilitating surgical removal. Timing of subsequent surgery is controversial. Some advocate waiting 7-10 days to permit tumor necrosis which simplifies resection[204, 205]. Complications include: hemorrhage (intratumoral and SAH), cranial nerve deficits (usually transient), CVA from embolization through ICA or VA anastomoses, scalp necrosis, retinal embolus, and potentially dangerous tumor swelling. Some meningiomas (e.g. olfactory groove) are less amenable to embolization.

Plain x-rays

May show: calcifications within the tumor (in ≈ 10%), hyperostosis or blistering of the skull (including floor of frontal fossa with olfactory groove meningiomas), enlargement of vascular grooves (especially middle meningeal artery).

TREATMENT

Surgery is the treatment of choice for symptomatic meningiomas. Incidental meningiomas with no brain edema or those presenting only with seizures that are easily controlled medically may be managed expectantly with serial imaging as meningiomas tend to grow slowly, and some may “burn out” and cease growing

(*see* *page 615*).

SURGICAL TECHNIQUE

Often very bloody. Preoperative embolization and autologous blood donation may be helpful. General principles of meningioma surgery[206]:

1. early interruption of the blood supply to the tumor
2. internal decompression (using ultrasonic aspirator, cautery loops…)
3. dissection of the tumor capsule from the brain by cutting and coagulating vascular and arachnoid attachments while infolding the tumor into the area of decompression with minimal retraction on adjacent brain
4. removal of attached bone and dura when possible

Position

As usual, the head should be elevated ≈ 30° above the right atrium. For meningiomas involving the superior sagittal sinus (SSS):

• for tumors involving the anterior third of the SSS: supine semi-sitting position
• for tumors of the middle third of the SSS: lateral position with the side of the tumor <u>down</u>, the neck tilted 45° toward the upward shoulder
• for tumors of the posterior third of the SSS: prone position

Sinus involvement

IMHO Attempting to occlude or bypass the middle third of the superior sagittal sinus involved with meningioma is treacherous. Even in expert hands, there is significant risk of venous infarction/sinus occlusion with 8% morbidity and 3% mortality[189], and complete removal is still not assured[207]. Venous collaterals may be found in the dura adjacent to the sinus, and even the tumor itself may participate. It is almost always preferable to leave residual tumor (and use radiosurgery when appropriate) than to cause a venous infarction.

Alternatives for treatment of dural sinus involvement include:

1. superior sagittal sinus **(SSS)**
   A. if the tumor occludes the SSS, it has been suggested that the sinus can be resected carefully preserving veins draining into the patent portions of the sinus. ✖ However, this should be undertaken with great trepidation since patients still not infrequently develop venous infarcts, probably as a result of loss of minimal sinus flow and venous channels in the dura. Before ligating the sinus, the lumen should be inspected

for a tail of tumor within

B. partial occlusion of superior sagittal sinus:
   1. anterior to the coronal suture, the sinus may usually be divided safely
   2. posterior to the coronal suture, it must not be divided or else severe venous infarction will occur
      a. with superficial involvement (Type I, *Figure 21-1*, page 614), tumor may be dissected off the sinus with care to preserve patency
      b. with extensive involvement:
         i. sinus reconstruction: hazardous. Thrombosis rate using venous graft approaches 50%, and is close to 100% with artificial grafts (e.g. Gore-Tex) which should not be used
         ii. it may be best to leave residual tumor, and follow with CT or MRI. If the residual tumor grows, or if the Ki-67 score is high (*see page 616*), SRS may be used (SRS may also be used as initial treatment for tumors that are < 2.3-3 cm, *see page 774*)

2. transverse sinus **(TS)**: a patent dominant TS must not be suddenly occluded

Sphenoid wing, parasagittal or falx meningiomas (general principles)

Once tumor is exposed a partial internal debulking is performed. Then the point of attachment (to the falx or sphenoid bone) is peeled away using bipolar cautery to divide feeding vessels. Then the main portion of the tumor may be separated from brain, with the tumor being avascular once the vascular pedicle has been transected.

Parasagittal and falx meningiomas

The inferior portion of the tumor may adhere to branches of the anterior cerebral artery. Middle or posterior third tumors are exposed using a horseshoe incision based in the direction of the major scalp feeding vessels. The patient may be placed in a lateral position, or the sitting position may be used with doppler monitoring for air embolism (*see page 153*). Anterior third tumors are approached using a bicoronal skin incision with the patient supine. For tumors that cross the midline, burr holes are placed to straddle the SSS. For managing superior sagittal sinus involvement, *see above*.

Sphenoid wing meningiomas

A pterional craniotomy is utilized (*see page 160*). The neck is extended to allow gravity to retract the brain off of the floor of the skull.

Lateral sphenoid wing meningiomas: These tumors are often similar to convexity meningiomas. The head is turned 60° to the side (*see page 159*). The height of the skin incision and bone opening should be high enough to encompass the tumor.

Medial sphenoid wing meningiomas: A lumbar drain is used. The head is turned 30° off the vertical. Aggressive extradural removal of sphenoid wing is performed. An FTOZ approach may provide additional exposure. The sylvian fissure is split widely. The ICA and MCA are often encased by tumor (look for the appearance of “grooves” on the surface of the tumor on MRI, which indicates vessels, e.g. MCA). To locate the ICA, identify MCA branches and follow them proximally into the tumor. The optic nerve is best identified at the optic canal. Avoid excessive retraction of the optic apparatus. The deep portion of the tumor often has numerous small parasitic vessels from the ICA (which makes this part very bloody), and may also invade the lateral wall of the cavernous sinus (which creates risk of cranial nerve deficits with attempted removal). Therefore, the recommendation is to leave some tumor behind and use radiosurgery to deal with it.

Olfactory groove meningiomas

Approached via a bifrontal craniotomy (preserving the periosteum to cover the frontal air sinus and floor of frontal fossa at the end of the case). Small tumors may be approached via unilateral craniotomy on the side with the most tumor)[127 (p 3284)]. For large tumors, a lumbar CSF drain will help with brain relaxation[191]. The head is rotated 20° to one side to facilitate dissection of the anterior cerebral arteries and optic nerve while pre-serving visualization of both sides of the tumor involvement[208]. The neck is slightly extended. The dura is opened low, and the superior sagittal sinus is ligated and divided at this location. Amputation of the frontal pole should be done if necessary to avoid excessive retraction. Vascular feeding arteries come through the floor of the frontal fossa in the midline. Initially, the anterior tumor capsule is opened and the tumor debulked from within heading towards the floor of the frontal fossa to interrupt the blood supply. The posterior capsule of the tumor is dissected carefully as this portion of the tumor may encase branches of the anterior cerebral artery, and/or

optic nerves and chiasm. A large tumor with suprasellar extension usually displaces the optic nerve and chiasm inferiorly[191]. If necessary, the frontopolar branch and other small branches may be sacrificed without problem[209]. Post-op risks include CSF leak through the ethmoid sinuses.

Tuberculum sellae meningiomas

These tumors typically displace both optic nerves posteriorly and laterally[191]. Occasionally, the nerves are completely engulfed by tumor.

Cerebellopontine angle meningiomas

Usually arise from the meninges covering the petrous bone. May be divided into those that occur anterior to, and those that occur posterior to the IAC.

Foramen magnum meningiomas

Tumors arising from the posterior or posterolateral lip of the foramen magnum **(FM)** are removed relatively easily. Anterior and lateral FM tumors may be operated by the posterolateral approach, and for anterior tumors[193], a transcondylar approach may alternatively be used[210].

With meningiomas below the vertebral artery **(VA)**, the lower cranial nerves are displaced superiorly with the VA. However, when the tumor is above the VA, the position of the lower cranial nerves cannot be predicted[193].

Large tumors may adhere to or encase neurovascular structures, and these should be internally debulked and then dissected free.

Posterior suboccipital approach: Used for meningiomas arising from the posterior lip of the FM or slightly posterolateral.

The patient is positioned prone or three-quarter prone. Neck flexion should be kept to a minimum to avoid brainstem compression by the tumor[211]. The surgeon must remain vigilant for the PICA and vertebral arteries, which may be encased.

Radiation therapy (XRT)

Generally regarded as ineffective as primary modality of treatment. Many prefer not to use XRT for "benign" lesions. Efficacy of XRT in preventing recurrence is controversial (*see below* under *Recurrence*); some surgeons reserve XRT for malignant (invasive), vascular, rapidly recurring ("aggressive"), or non-

resectable meningiomas.

For recurrent atypical or anaplastic meningioma with residual disease: post-op, XRT with 55-60 Gy is recommended.

Table 21-25 Simpson grading system for removal of meningiomas[212]

Grade	Degree of removal
I	macroscopically complete removal with excision of dural attachment and abnormal bone (including sinus resection when involved)
II	macroscopically complete with endothermy coagulation (Bovie, or laser) of dural attachment
III	macroscopically complete without resection or coagulation of dural attachment or of its extradural extensions (e.g. hyperostotic bone)
IV	partial removal leaving tumor in situ
V	simple decompression (± biopsy)

OUTCOME

5 year survival for patients with meningioma[6]: 91.3%.

RECURRENCE

The extent of surgical tumor removal is the most important factor in the prevention of recurrence. The Simpson grading system for the extent of meningioma removal is shown in *Table 21-25*. Recurrence after gross total tumor removal occurred in 11-15% of cases, but was 29% when removal is incomplete (length of follow-up not specified)[186]; 5-year recurrence rates of 37%[213]-85%[214] after partial resection are also quoted. The overall recurrence rate at 20 years was 19% in one series[215], and 50% in another[214]. Malignant meningiomas have a higher recurrence rate than benign ones.

Value of XRT

A retrospective series of 135 non-malignant meningiomas followed 5-15 years postop at UCSF revealed a recurrence rate of 4% with total resection, 60% for partial resection without XRT, and 32% for partial resection with XRT[216]. Mean time to recurrence was longer in the XRT group (125 mos) than in the non-XRT group (66 mos). These results suggest that XRT may be beneficial in partially resected meningiomas. Alternatively, one can follow these patients with CT or MRI and use XRT for progression.

In addition to the usual side effects of XRT (see *Radiation injury and*

necrosis, page 771), there is also a case report of a malignant astrocytoma developing after XRT was used to treat a meningioma[217].

21.2.7. Mesenchymal, non-meningothelial tumors

Hemangiopericytoma

A sarcoma arising from pericytes (surrounding blood vessels). May metastasize (usually to bone, lung or liver). Occur ≈ anywhere (soft tissues, muscles, thoracic aorta, kidney, omentum…). May mimic meningioma on CT or MRI (MRS may help distinguish[218]). Recurrence is common, sometimes late. Neurosurgically relevant sites:

1. intracranial: includes intraventricular
2. spinal

Treatment: Surgery is primary treatment. XRT may reduce recurrence rate. Chemo-therapy is used for metastases or for tumors failing local control measures.

Primary cerebral sarcoma

Rare. May result from sarcomatous change in preexisting tumor such as meningioma, glioblastoma, or oligodendroglioma.

21.2.8. Vestibular schwannoma

Key concepts:

- histologically benign tumor. Usually arises from superior vestibular nerve in CPA
- 3 most common early symptoms (clinical triad): hearing loss (insidious and progressive), tinnitus (high pitched) and dysequilibrium (true vertigo is uncommon)
- W/U: All patients: ✔ MRI (without & with contrast), ✔ audiometrics (pure tone audiogram and speech discrimination). In addition for small VSs (≤ 15 mm dia): ✔ ENG, ✔ VEMP, ✔ ABR
- histology: comprised of Antoni A (narrow elongated bipolar cells) and Antoni B fibers (loose reticulated)

- management options (observation, surgery, XRT or chemotherapy (Avastin®)) depend heavily on tumor size, growth, hearing status, and presence of NF2

Vestibular schwannoma is currently preferred[220, 221] over the older term acoustic neuroma since most of these tumors arise not from the acoustic nerve but from the schwann-cell sheath of the superior division of the vestibular nerve (not the cochlear portion). Histologically benign. VSs arise as a result of the loss of a tumor-suppressor gene on the long arm of chromosome 22 (in sporadic cases this is a somatic mutation; in neurofibromatosis Type 2 **(NF2)** this is either inherited or represents a new mutation that may then be transmitted to offspring).

Epidemiology: One of the most common intracranial tumors, comprising 8-10% of tumors in most series[222]. Annual incidence is probably about 1.5 cases per 100,000 population - over the past couple decades this estimate has increased and the typical size at diagnosis has decreased as a result of the proliferation of MRI scans[223]. VSs typically become symptomatic after age 30. At least 95% are unilateral.

Neurofibromatosis Type 2

The incidence of vestibular schwannomas **(VS)** is increased in neurofibromatosis **(NFT)**, with bilateral VS being pathognomonic of neurofibromatosis Type 2 **(NFT2)** (central NFT, *see page 724*). Any patient < 40 yrs old with unilateral VS should also be evaluated for NFT2. Cytologically, the VSs of NFT2 are identical to sporadic cases, however in NFT2 the tumors form grape-like clusters that may infiltrate the nerve fibers (unlike most sporadic VSs which displace the eighth nerve).

Clinical

Symptoms

Symptoms are shown in *Table 21-26*. The type of symptoms are closely correlated with tumor size. Most initially cause the triad of ipsilateral sensorineural hearing loss, tinnitus and balance difficulties. Larger tumors can cause facial numbness, weakness or twitching, and possibly brainstem symptoms. Rarely, large tumor may produce hydrocephalus. With current imaging modalities (CT and especially MRI), increasing numbers of smaller

lesions are being detected.

Table 21-26 Symptoms in vestibular schwannoma (131 patients[222])

Symptom	%
hearing loss	98%
tinnitus	70%
dysequilibrium*	67%
H/A	32%
facial numbness	29%
facial weakness	10%
diplopia	10%
N/V	9%
otalgia	9%
change of taste	6%

* or vertigo

Symptoms from 8th nerve compression

Unilateral sensorineural hearing loss, tinnitus and dysequilibrium are related to pressure on the eighth nerve complex in the IAC. These are the earliest symptoms, and by the time of diagnosis, virtually all tumors have caused otologic symptoms.

Hearing loss is insidious and progressive in most (c.f. the hearing loss in Meniere's disease which fluctuates), however 10% report sudden hearing loss (see *Sudden hearing loss* below). 70% have a high frequency loss pattern, and word discrimination is usually affected (especially noticeable in telephone conversation).

The tinnitus is usually high pitched.

Unsteadiness manifests primarily as balance difficulty; true vertigo occurs in < 20%.

Sudden hearing loss: The differential diagnosis for sudden hearing loss **(SHL)** is extensive[224]. *Idiopathic* SHL (i.e. no identified etiology: must rule out neoplasm, infection, autoimmune, vascular and toxic causes) occurs in an estimated 10 per 100,000 population[225]. 1% of patients with SHL will be found to have a VS, and SHL may be the presenting symptom in 1-14% of patients

with VS[226]. SHL with VS is presumably due to an infarction of the acoustic nerve, or acute occlusion of the cochlear artery. Treatment options for SHL include:

1. steroids: e.g. prednisone 60 mg PO q d **x** 10 d then tapered[226]
2. ✖ heparin has been shown not to be of help
3. conservative treatment: rest, restriction of salt, alcohol and tobacco[227]
4. experimental: thrombolytic therapy (e.g. rt-PA) (*see page 1016*)

Symptoms from 5th and 7th nerve compression

Otalgia, facial numbness and weakness, and taste changes occur as the tumor enlarges and compresses the fifth and seventh nerves. These symptoms usually do not occur until the tumor is > 2 cm. This highlights an interesting paradox: facial weakness is a rare or late occurrence, even though the 7th nerve is almost always distorted early; whereas facial numbness occurs sooner once trigeminal compression occurs (often in the presence of normal facial movement), despite the fact that the 5th nerve is farther away[228]. This may be due to the resiliency of motor nerves relative to sensory nerves.

Symptoms from compression of brainstem and other cranial nerves

Larger tumors cause brainstem compression (with ataxia, H/A, N/V, diplopia, cerebellar signs, and if unchecked, coma, respiratory depression and death) and lower cranial nerve (IX, X, XII) palsies (hoarseness, dysphagia…). Obstruction of CSF circulation by larger tumors (usually > 4 cm) may produce hydrocephalus with increased ICP.

Rarely, 6th nerve involvement may cause diplopia.

SIGNS

Hearing loss due to VIII involvement is the earliest cranial nerve finding. 66% of patients have no abnormal physical finding except for hearing loss (for other findings, see *Table 21-28*).

Since hearing loss is sensorineural, **Weber test** will lateralize to the uninvolved side, and if there is enough preserved hearing, **Rinne test** will be positive (i.e. normal; air conduction > bone conduction) on both sides (*see page 848* for these tests).

Table 21-27 Clinical grading of facial nerve function (House and Brackmann[229])

Grade	Function	Description
1	normal	normal facial function in all areas
2	mild dysfunction	1. gross: slight weakness noticeable on close inspection; may have very slight synkinesis 2. at rest: normal symmetry and tone 3. motion: A. forehead: slight to moderate movement B. eye: complete closure with effort C. mouth: slight asymmetry
3	moderate dysfunction	1. gross: obvious but not disfiguring asymmetry: noticeable but not severe synkinesis 2. motion: A. forehead: slight to moderate movement B. eye: complete closure with effort C. mouth: slightly weak with maximal effort
4	moderate to severe dysfunction	1. gross: obvious weakness and/or asymmetry 2. motion: A. forehead: none B. eye: incomplete closure C. mouth: asymmetry with maximum effort
5	severe dysfunction	1. gross: only barely perceptible motion 2. at rest: asymmetry 3. motion: A. forehead: none B. eye: incomplete closure
6	total paralysis	no movement

Table 21-28 Signs in 131 vestibular schwannomas (excluding hearing loss)[222]

Sign	%
abnormal corneal reflex	33
nystagmus	26
facial hypoesthesia	26
facial weakness (palsy)	12
abnormal eye movement	11
papilledema	10
Babinski sign	5

Facial nerve (VII) dysfunction is uncommon before treatment. When present, it is usually graded clinically on the House and Brackmann scale (*see Table 21-27*).

Vestibular involvement causes nystagmus (may be central or peripheral) and abnormal electronystagmography (ENG) with caloric stimulation.

DIFFERENTIAL DIAGNOSIS

See *Cerebellopontine angle (CPA) lesions* on page 1210. The major differentials are: meningioma, or neuroma of an adjacent cranial nerve (e.g. trigeminal).

PATHOLOGY

Tumors are composed of **Antoni A** fibers (narrow elongated bipolar cells) and **Antoni B** fibers (loose reticulated). **Verocay** bodies are also seen, and consist of acellular eosinophilic areas surrounded by parallel arrangement of spindle shaped schwann cells.

EVALUATION

1. brain MRI without and with contrast. FIESTA MRI if available. If MRI is contraindicated, then a CT scan without and with contrast
2. audiometric evaluation:
   A. pure tone audiogram (*see below*)
   B. speech discrimination evaluation (*see below*)
   C. patients with small VSs (≤ 15 mm dia) also get:
      1. ENG: assesses superior vestibular nerve (*see page 624*)
      2. VEMP: assesses inferior vestibular nerve (*see page 624*)
      3. ABR: prognosticates chance of hearing preservation (*see page 624*)

AUDIOMETRIC AND AUDIOLOGIC STUDIES

Baseline studies are helpful for management treatment decisions and for later comparison and to assess the contralateral ear.

Pure tone audiogram (PTA)

May be useful as first-step screening test. Air conduction assesses the entire system, bone conduction assesses from the cochlea and proximally. PTA assesses the functionality of hearing (to help in treatment decision making) and acts as a baseline for future comparison. The single numerical score is an average of the thresholds for frequencies across the audio spectrum. On a standard audiogram, X's denote the left ear (AS) and O's denote the right ear (AD).

Progressive unilateral or asymmetric sensorineural hearing loss of high tones occurs in > 95% of VSs[230]. High-frequency hearing loss also happens to be the most common type of hearing loss with age or with noise induced sensorineural

hearing loss, but is usually symmetrical. Only ≈ 1 in 1000 patients with asymmetric hearing have a VS[220]. Other causes of asymmetrical sensorineural hearing loss[231]: other CPA lesions (e.g. meningioma), inner ear lesions, intraaxial lesions (including 9 infarctions), multiple sclerosis. On hearing screening tests, an unexplained PTA difference from one ear to the other > 10-15 dB is suspicious and should be investigated further.

Speech discrimination evaluation

Speech discrimination is maintained in conductive hearing loss, moderately impaired in cochlear hearing loss, and worst with retrocochlear lesions. No longer used for diagnostic purposes (a score of 4% suggests a retrocochlear lesion, as does a score that is worse than would be predicted based on PTA testing (the speech recognition threshold should be similar to PTA thresholds below 4 kHz)). Has found usefulness in determining serviceability of hearing and prognosticating for hearing preservation surgery. Open-set **word recognition score (WRS)** (*see Table 21-29*) is a more sensitive measure of communication ability than PTA.

Table 21-29 Open-set word recognition score

Class	WRS%
I	70-100%
II	50-69%
III	1-49%
IV	0

Definition of serviceable hearing

There are many definitions of what constitutes serviceable hearing. Also, even non-serviceable hearing can offer some benefit. If WRS is good (≥ 70%) but PTA is poor, a hearing aid may provide significant benefit.

Some definitions of **serviceable hearing** (*see text* that follows for details):

1. AAO-HNS class A or B
2. "50/50 rule": Gardner-Robertson class I or II (pure tone audiogram threshold ≤ 50 dB and speech discrimination score ≥ 50%)
3. some prefer a 70/30 rule (70% WRS, 30 dB PTA)
4. in a patient with good hearing in the contralateral ear, a speech

discrimination score **(SDS)** of < 70% in the affected ear is not considered good hearing; whereas if the contralateral ear is totally deaf, a SDS of ≥ 50% can be useful[232]

Modified **Gardener-Robertson** system for grading hearing: shown in *Table 21-30*. Class I patients may use a phone on that side, class II patients can localize sounds.

The American Academy of Otolaryngology - Head and Neck Surgery Foundation **(AAO-HNS)** hearing classification system[233]: shown in *Table 21-31*.

Table 21-30 Gardener and Robertson modified hearing classification*

Class	Description	Pure tone audiogram† (dB)	Speech discrimination†
I	good-excellent	0-30	70-100%
II	serviceable	31-50	50-59%
III	nonserviceable	51-90	5-49%
IV	poor	91-max	1-4%
V	none	not testable	0

* modification[234] of the Silverstein and Norrell system[235]

† if PTA and speech discrimination score do not qualify in the same class, use the lower class

NB gray shading (class ≥ III) is generally considered non-serviceable hearing

Table 21-31 American Academy of Otolaryngology-Head and Neck Surgery Foundation hearing classification system

Class	Pure tone threshold (dB)*		Speech discrimination score† (%)
A	≤ 30	AND	≥ 70
B	> 30 AND ≤ 50	AND	≥ 50
C	> 50	AND	≥ 50
D	any level		< 50

* average of pure tone hearing thresholds by air conduction at 0.5, 1, 2 & 3 kHz

† speech discrimination at 40 dB or maximum comfortable loudness

NB class A & B are considered "useful", class C is "aidable", & class D is nonfunctional

Additional tests that are helpful with small VSs (≤ 15 mm diameter)

The ENG and VEMP evaluate the superior and inferior division of the vestibular nerve **(VN)** respectively. The inferior VN is closer to the cochlear nerve than the superior VN (see *Figure 5-7*, page 90), and small tumors (≤ 4 mm) of the inferior VN tend to be deeper and closer to the cochlear nerve than similar sized tumors of the superior division which tend to be more superficial and more easily removed.

Electronystagmography (ENG): Only tests the horizontal semicircular canal ∴ assesses the <u>superior</u> vestibular nerve which innervates it. Normally, each ear contributes an equal portion of the response. The ENG is considered abnormal if there is > 20% difference between the two sides. Response may be normal with a small tumor arising from the <u>inferior</u> division of vestibular nerve. NB: the vestibular nerve may continue to function until almost all of the nerve fibers are affected.

Vestibular evoked myogenic potential (VEMP): Assesses <u>inferior</u> vestibular nerve by testing the saccule[236]. Independent of hearing (can be done even with severe sensorineural hearing loss).

Auditory brainstem responses (ABR): AKA **BAER** (*see page 267*). The most common findings are prolonged I-III and I-V interpeak latencies. No longer used for diagnostic purposes (sensitivity is only ≈ 88-90% (i.e. will miss 10-12% of VSs) and specificity is only 85%. ABR is useful for prognostication - poor wave morphology correlates with lower chance of preserving hearing (even with good hearing).

Radiographic evaluation

MRI: Thin slice axial plane gadolinium enhanced MRI is the diagnostic procedure of choice with sensitivity close to 98% and almost 0% false positive rate. Characteristic findings: round or oval enhancing tumor centered on IAC. Large VSs (> 3 cm dia) may show cystic appearing areas on CT or MRI; in actuality these areas are usually solid. Adjacent trapped CSF cisterns may also give cystic appearance.

FIESTA MRI (fast imaging employing steady state acquisition): uses CSF as the contrast agent (∴ does <u>not</u> use gadolinium).

CT scan: CT with IV contrast is second choice for imaging modality. If normal, and clinical suspicion of VS is strong, small lesions may be visualized by introducing 3-4 ml of subarachnoid air via lumbar puncture, and scanning the patient with the affected side up (to trap air in region of IAC), non-filling of the

IAC is indicative of an intracanalicular mass. Even with air contrast, CT was normal in 6% in Mayo series[222]. Although many VSs enlarge the ostium of the IAC (called trumpeting) (normal diameter of the IAC is = 5-8 mm), 3-5% of VSs do not enlarge the IAC on CT; this percent may increase as patients are scanned earlier with smaller tumors. Advantage over MRI: shows bony anatomy (including mastoid air cells) which is often helpful for planning translabyrinthine approach.

MANAGEMENT

Options for management include:

1. **expectant management**: follow symptoms, hearing (audiometrics) and tumor growth on serial imaging (MRI or CT). Intervention is performed for progression. Growth patterns observed:
   A. little or no growth: applies to most (83%) VSs confined within the IAC and 30% extending into CPA (see *natural history of growth* below)
   B. slow growth ≈ 2 mm/yr
   C. rapid growth: ≥ 10 mm/yr
   D. a few actually shrink[223]
2. **radiation therapy** (alone, or in conjunction with surgery)
   A. external beam radiation therapy **(EBRT)**
   B. stereotactic radiation
      1. stereotactic radiosurgery **(SRS)**: single dose (*see page 775*)
      2. stereotactic radiotherapy **(SRT)**: fractionated (*see page 776*)
3. **surgery**: approaches include the following (*see below* for details)
   A. retrosigmoid (AKA suboccipital): may be able to spare hearing
   B. translabyrinthine (and its several variations): sacrifices hearing, may be slightly better for sparing VII
   C. middle fossa approach (extradural subtemporal): only for small lateral VSs
4. **chemotherapy**: some early promise for NF2-related vestibular schwannomas with bevacizumab (Avastin®), an anti-VEGF (vascular endothelial growth factor) monoclonal antibody. In 6 such patients, 4 had radiographically significant tumor shrinkage and 4 had improvement in auditory word recognition score[237]

Patient/tumor factors influencing management decisions

In addition to the usual factors involved in the decision process with brain tumors, e.g. the patient's general medical condition, age, natural history, etc., elements unique to VSs include: chances of preserving VII & V nerve function and hearing (in those with serviceable hearing) (all of which are related to tumor size), and the presence of NF2.

Specifics:

1. natural history of growth
   A. usual quoted range: ≈ **1-10 mm/yr**. However this can be quite variable
   B. strictly intracanalicular tumors: only 17% grew outside the meatus[A]
   C. extrameatal tumors (with extension into CP angle): 30% grew > 2 mmA
   D. VSs that did not grow in the 5 years after diagnosis did not grow after that
   E. 6% actually decrease in size[238]
2. natural history of hearing function in untreated intracanalicular VSs in AAOHNS Group A (*see Table 21-31*) patients[239]
   A. 50% deteriorated to a lower class over 4.6 years (loss of ≥ 10 dB PTA or ≥ 10% SDS)
   B. after 4.6 years of observation, the proportion of patients eligible for hearing preservation treatment (as determined by a word recognition score class I (70-100% SDS)) was reduced to 28% (a 44% reduction) and by AAO-HNS class A to 9% (a 53% reduction)
   C. the risk of losing hearing was not related to: age, gender, acoustic tumor size (all tumors were intracanalicular) or tumor sublocalization (fundus, central, porus)
   D. hearing loss was positively correlated to the absolute volumetric tumor growth rate (tumors that eventually expand out of the IAC have a faster rate and degree of hearing loss compared to tumors remaining in the IAC
   E. the risk of losing hearing was significantly lower for patients with 100% word recognition score. Over 4.6 years observation, 89% remained in WRS class I (*see Table 21-29*) compared to only 43% for patients with only a small (1-10%) loss of WRS at diagnosis
3. size: as tumors exceed **15 mm** diameter, treatment complications increase

   A. significantly lower chance for hearing preservation
   B. increased incidence of VII injury
4. presence of cysts: cystic tumors may display sudden and dramatic growth[223]
5. serviceable hearing: see *Definition of serviceable hearing*, page 623
6. hearing in contralateral ear

A. in 522 VSs over 3.6 years mean follow-up 223

Management algorithm

1. intracanalicular or CPA tumors ≤ 20 mm diameter that are noncystic & non-NF2: observation with serial imaging and hearing tests ("wait and scan" scheme). Follow-up schedule
   A. imaging: F/U CT or MRI (treatment for > 2 mm growth between studies)
      1. q 6 mos **x** 2 yrs (i.e. 1 & 2 years after diagnosis)
      2. if stable, then annually until year 5 after diagnosis
      3. if stable, then at years 7, 9 & 14 after diagnosis[223]
   B. annual audiology evaluations: in patients with small tumors and normal SDS, comparing the results of hearing preservation with surgery or SRS to the natural history, the conclusion is that established tumor growth should be the main determinant for treatment[232]
2. tumors > 15-20 mm should be treated[223, 232]. However, this also must take into account the patient's age, hearing…
3. NF2 patients present a challenge and should be evaluated individually. In general the success rate in the management of their tumors is lower (higher cranial nerve deficit and higher recurrence rate)[240, 241]. Early management is considered more favorable for good outcome[242]. Recent attempts with chemotherapy using bevacizumab (Avastin®) appears to be a promising albeit still investigational option[237] (*see above*)

Selection of treatment option

Comparison of microsurgery vs. radiosurgery **(SRS)**

1. hearing preservation

A. for patients with testable pre-operative hearing
   1. **summary**: radiosurgery or stereotactic radiation appears to be better at preserving hearing than microsurgery. The difference is minor for tumors < 10 mm and very good pre-operative hearing (70% SDS, and 30 dB PTA). The advantage of radiation is more pronounced for larger tumors and greater pre-operative hearing loss. Details:
   2. **SRS**: overall, at 3, 5, and 10 years, 81%, 77% and 66% of the patients maintained their GR hearing class (see *Table 21-30*, page 623). For patients receiving a tumor margin dose of 13 Gy or less, those same percentages were 93%, 87% and 87% 243. Hearing preservation appears to be related to the radiation dose to the cochlea rather than to the tumor itself[244]
   3. **microsurgery**: hearing preservation is significantly related to the tumor size and to the experience of the surgical team. Hearing preservation in Samii's series of 1000 VS[241] improved from 24% in the first 200 cases to 49% in later cases. Hearing preservation in microsurgery has improved with the use of direct cochlear nerve monitoring[245] compared to auditory brainstem responses monitoring only. Hearing preservation in patients with class A, small tumors and direct cochlear nerve monitoring (compound nerve action potential) was 91%[246]

2. facial nerve preservation
   A. preservation has been excellent with both microsurgery and radiosurgery
   B. **microsurgery**: 98.5% overall[247] and 100% in tumors not touching the brainstem. Staged resection has been advocated by some to improve facial nerve preservation in giant VS (> 4-4.5 cm)[248]
   C. **radiosurgery**: 98% of patients[243]. The incidence of facial neuropathy has significantly decreased since the SRS dose was decreased to 12-13 Gy. Facial neuropathy in the recent series occurred in patients having received 18-20 Gy
3. trigeminal neuropathy **(TGN)**
   A. a complication classically feared in large tumors especially following SRS
   B. **SRS**: 7% incidence of TGN (mainly in patients receiving higher doses, i.e. 18 Gy). No patients who received a dose < 13 Gy developed

TGN[243]

C. **microsurgery**: post-op TGN is not reported in most series

4. tumor control (local control rates **(LCR)**):

   A. tumor control has been a concern with radiosurgery and with the more recent decrease in dose from 18-20 Gy to 12-14 Gy, long term data are lacking

   B. **microsurgery**: tumor recurrence has been poorly studied. Quoted rates in the literature vary between 0.5% at 6 years[247] to 9.2%[249]

   C. **SRS**: tumor recurrence requiring retreatment at 5 years was 4%[243] but 18% of patients presented with transient increase in the size of the tumor ("pseudogrowth") at a mean of 8 months, with later regression in half and stabilization to the new size in the other half

Vertigo: For patients with episodic vertigo or balance difficulties as the predominant symptom (also, see points under *Selection of treatment option* on page 625):

1. remember: patients with VS are susceptible to other causes of vertigo as well, and patients should undergo ENG and functional balance assessment
2. vertigo that is due to the VS is often self-limited, and improves in 6-8 weeks to a reasonably tolerable level with no treatment (patients may do better with so-called "vestibular rehab")
3. residual dizziness and balance disturbances are common whether stereotactic radiosurgery **(SRS)** or microsurgery **(MS)** is used, but are typically less after MS
4. after SRS: beneficial effects require a minimum of 5-6 mos, and sometimes may require up to eighteen months
5. following MS: symptoms are usually immediately worsened, but then gradually improve in most cases (except perhaps when the balance difficulties are due to brainstem compression). Symptoms are improved more rapidly than with SRS
6. **conclusion**: observation may be the best choice for ≈ 20% of patients. When treatment is desired, surgery is the best choice for most VSs producing vertigo. SRS may be the right choice for some, especially: elderly patients (> 70 yrs) with other health problems, for recurrence of VS, and for individual preference

Hydrocephalus: When hydrocephalus is present, it may require separate treatment with a CSF shunt (see *Surgical considerations*, page 627), and may

possibly be done at the same time as surgery for the VS (if indicated).

SURGICAL TREATMENT

Approaches

Three basic surgical approaches:

1. those with possibility of hearing preservation
   A. middle fossa **(MF)**: poor access to posterior fossa (*see below*)
   B. retrosigmoid **(RS)** (*see page 628*) AKA retrosigmoid-transmeatal approach
2. translabyrinthine **(TL)**: non hearing preserving (*see below*)

Excellent results have been reported with each of these approaches. These guide-lines assume that the surgical team is comfortable with all three approaches.

Decision algorithm:

The choice of approach is dictated by hearing salvageability and tumor size as follows:

1. **salvageable hearing** (*see Table 21-32* for definition and guidelines)
   A. if tumor is intracanalicular (no extension beyond a few mm into the posterior fossa (CPA)[A]): **middle fossa** approach
   B. if tumor extends > few mm into the posterior fossa: **retrosigmoid** approach
2. **non salvageable** hearing (*see Table 21-32* for definition and guidelines)
   A. **translabyrinthine approach** for most
   B. if the neurotologist feels that the tumor is too large to remove via a translabyrinthine approach[B]: **retrosigmoid approach**

A. differences of opinion exist regarding how much tumor in the CPA can be removed via MF
B. may be due to a small presigmoid space and/or a large tumor

Table 21-32 Hearing salvageability

Definition of serviceable hearing
A generous definition of serviceable hearing: PTA < 50 dB and SDS > 50%*

Unsalvageable hearing
Serviceable hearing is <u>unlikely</u> to be preserved post-op when
1. pre-op SDS < 75%
2. or pre-op PTA loss > 25 dB
3. or pre-op BAER has abnormal wave morphology
4. or tumor > 2-2.5 cm diameter

* for other definitions of serviceable hearing see page 623

SURGICAL CONSIDERATIONS

The superior vestibular division of VIII is the usual origin of the tumor. The facial nerve is pushed forward by the tumor in ≈ 75% of cases (range: 50-80%), but may occasionally be pushed rostrally, less often inferiorly, and rarely posteriorly. It may even continue to function while it is flattened to a mere ribbon on the tumor capsule surface.

Anesthesia with minimal muscle relaxants allows intra-op seventh nerve monitoring. In only ≈ 10% of large tumors is the cochlear nerve a separate band on the tumor capsule, in the remainder it is incorporated into the tumor.

Total excision of tumor is usually the goal of surgery. The only indications for planned subtotal resection is a large tumor on the side of the only ear with good hearing or those patients requiring debulking with little chance of recurrence because of limited life expectancy, especially if the facial nerve is densely adherent to the tumor[250, 251].

If hydrocephalus is present, it used to be standard practice to place a CSF shunt and wait ≈ 2 weeks before the definitive operation[252]. While still acceptable, this is less commonly done at present.

- large tumors may be approached by a combined translab-retrosigmoid approach to debulk tumor and preserve facial nerve; a two stage approach (with 1-2 weeks in between) may improve results with very large tumors[253]

MIDDLE FOSSA APPROACH

- indications:
  - A. hearing preservation
  - B. laterally placed tumors
  - C. small tumors (usually < 2.5 cm)
- pros:
  - A. allows drilling and exposure of the IAC all the way to the geniculate ganglion (good for laterally placed tumors)

B. basically an extradural subtemporal operation

• cons:

A. potential damage to temporal lobe with risk of seizures

B. facial nerve is the most superficial nerve in this exposure and therefore the surgeon works “around” the facial nerve (possibility of injury)

• technique summary

A. lumbar drain

B. usually straight incision, starting in front of the tragus, extending cephalad for 6 cm, held open with a self retaining retractor

C. the temporalis muscle is incised vertically (along the muscle fibers) along the most posterior aspect of the exposure, as well and reflected anteriorly

D. craniotomy: 4 cm x 3 cm

E. elevate the middle fossa dura, section the middle meningeal artery. Identify and preserve the greater superficial petrosal nerve **(GSPN)**, arcuate eminence, V3, and true edge of the petrous bone (the false edge is the groove occupied by the superior petrosal sinus

F. drill and expose the internal auditory canal all the way to Bill’s bar (for tumors extending laterally)

G. localize the facial nerve with the nerve stimulator

H. open the IAC dura along the main axis of the IAC, avoiding VII

I. identify the vestibular, cochlear and facial nerves

J. dissect the tumor off the nerves

TRANSLABYRINTHINE APPROACH

Especially useful for tumors with primarily intracanalicular component with little CPA extension. Often preferred by neurootologists.

• pros & cons: *see Table 21-33*

• technique summary

A. skin incision should be tailored to the location of the sigmoid sinus (observe location of the sigmoid sinus and pinna of the ear on the pre-op MRI). Usually smaller opening than retrosigmoid approach

B. does not require a craniotomy. For large tumors requiring an “extended translab”, 1-2 cm of retrosigmoid dura should be exposed during the mastoidectomy to allow for retraction of the sigmoid sinus

C. dural opening along the IAC after identification of VII with stimulator

D. for large tumor: section the superior petrosal sinus and section the tentorium to gain better intradural exposure

E. closure requires fat graft

Table 21-33 Pros & cons of translab approach

Disadvantages	Advantages
• sacrifices hearing (acceptable when hearing is already nonfunctional or unlikely to be spared by other approach) • limited exposure (limits maximal tumor size that can be approached) • may take longer than retrosigmoid approach • possibly higher rate of post-op CSF leak	• early identification of VII may result in higher preservation rate • less risk to cerebellum and lower cranial nerves • patients do not get as "ill" from blood in cisterna magna, etc. (essentially an extracranial approach)

Retrosigmoid approach

AKA posterior fossa, AKA suboccipital approach[254, 255].

• pros:

A. familiar to most neurosurgeons ∴ often preferred by neurosurgeons

B. quick access to the tumor

C. hearing preservation possible

D. NOTE: this approach is very versatile. Samii[241] resected all his acoustic tumors via a retrosigmoid approach[A]

• cons:

A. cerebellar retraction: not a problem for tumors < 4 cm, provided the craniotomy is sufficiently lateral and the cisterna magna and the CP angle cistern has been opened

B. headaches: it has been suggested that headaches are more common in retrosigmoid craniotomy than in the translabyrinthine craniotomy

---

A. he achieved a significant amount of brain relaxation and improved exposure by using in the sitting position, which is generally not used in the USA because of associated complications (*see page 153*)

Booking the case - retrosigmoid craniotomy for vestibular schwannoma

Also see defaults & disclaimers (*page v*).

1. position: supine with shoulder roll

2. equipment:
   A. microscope
   B. ultrasonic aspirator
   C. image guided navigation system (if used) (may be helpful for placing skin incision and craniotomy more than for tumor localization except with large tumors)
3. some surgeons use ENT to assist with the IAC and for follow-up
4. neuromonitoring: facial EMG (does not require EEG tech), direct cochlear nerve monitoring and SSEPs (if used, requires EEG tech)
5. post op: ICU
6. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through an incision behind the ear to remove a tumor in the skull on the nerve to the ear; possible need for post-op lumbar drain
   B. alternatives: nonsurgical management with follow-up MRIs, other surgical approaches, radiation (stereotactic radiosurgery)
   C. complications: CSF leak with possible meningitis, loss of hearing in ipsilateral ear (if not already lost), paralysis of facial muscles on the side of surgery with possible need for surgical procedures to help correct (correction is often far from perfect), post-op balance difficulties/vertigo, brainstem injury with stroke

Technique summary

1. position: 30° elevation of the head is paramount (see *Posterior fossa (suboccipital) craniectomy*, *Lateral oblique position* on page 154)
2. percutaneous lumbar drain (optional)
3. incision is shaped like the pinna of the ear, 3 finger breaths behind the external auditory canal
4. the craniotomy has to be lateral enough to expose part of the sigmoid and part of the transverse sinuses.
5. to prevent CSF leak, seal all bone edges with bone wax
6. dural opening along the lines of the craniotomy
7. exposure is enhanced by opening the cerebello-pontine angle cistern and the cisterna magna under the microscope and draining CSF (20-40 ml of CSF can also be drained via a lumbar subarachnoid catheter)
8. the petrosal vein is often sacrificed at the beginning of the procedure to

allow the cerebellum to relax and fall back and to avoid tearing off the transverse sinus. Be careful not to coagulate the SCA that often runs with the petrosal vein

9. using the facial nerve stimulator, the posterior aspect of the tumor is inspected to make sure the facial nerve has not been pushed posteriorly
10. the thin layer of arachnoid that covers most tumors is identified. Vessels within the arachnoid may contribute to cochlear function and may be preserved by keeping them with the arachnoid
11. the plane between tumor and cerebellum may be followed to the brainstem, and occasionally to the VII nerve (this plane is harder to follow once bleeding from tumor debulking occurs)
12. to help locate the origin of the VII nerve at the brainstem see *Table 21-34* and CPA anatomy in *Figure 5-8*, page 90
13. the posterolateral tumor capsule is opened, and internal decompression is performed. The tumor is collapsed inward and the capsule is kept intact and is rolled laterally off of VII and is eventually removed. The most difficult area to separate VII from tumor is just proximal to the entrance to the porus acusticus

Table 21-34 Aids in localizing VII nerve origin[256]

• VII nerve originates in the pontomedullary sulcus near the lateral end of the sulcus, 1-2 mm anterior to the VIII nerve
• the pontomedullary sulcus ends just medial to the foramen of Luschka (extending from the lateral recess of the IV ventricle) *see Figure 5-8*
• a tuft of choroid plexus usually extends out of the foramen of Luschka on the posterior surface of IX and X nerve, just inferior to the origin of VII
• the flocculus of the cerebellum projects from the lateral recess into the CPA just posterior to the origin of VII and VIII
• VII origin is 4 mm cephalad and 2 mm anterior to that of the IX nerve

NB: large tumors: in some large tumors, the capsule may be adherent to the brainstem and so portions of tumor must be left; recurrence rate among these is ≈ 10-20%[127]. Large tumors may also involve V superiorly (sometimes VII is pushed up against V), and inferiorly may involve IX, X, and XI. The lower cranial nerves can usually be spared by dissecting them off of the tumor capsule, and protecting them with cottonoids.

14. after the extracanalicular portion of tumor is removed, the dura over the IAC is incised, and the IAC is drilled open and tumor is removed from this portion. To preserve hearing, the bony labyrinth must not be violated. The

posterior semicircular canal **(SCC)** is the most vulnerable structure (*see Figure 21-2*). The vestibule of the SCCs is also at risk but is less likely to be entered. The maximal amount of temporal bone drilling that can be accomplished without entering the posterior SCC can be determined from the pre-op CT. There is no exact anatomical landmark, some say that the IAC must <u>not</u> be opened lateral to the transverse crest which is ≈ 1 cm deep within the IAC, others recommend measuring the distance to the SCC on a pre-op CT and not opening the lateral 1-2 mm of the IAC[257]. However, opening the labyrinth cannot always be avoided; and any opening should be plugged with bone-wax or muscle[257]. If the facial nerve is not intact and is not going to be grafted, then the IAC should be plugged, e.g. by bone wax covered with a small piece of hammered muscle (hammering makes the muscle sticky by activating extrinsic clotting factors) and Gelfoam®.

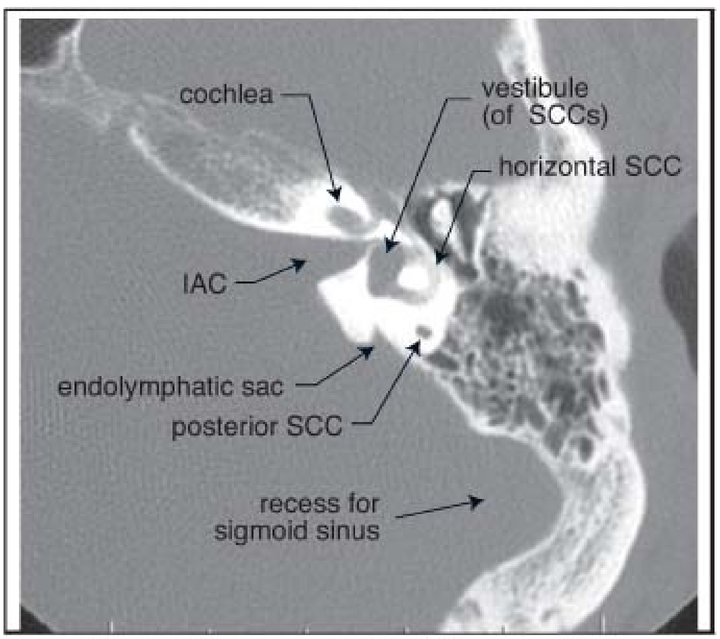

Figure 21-2 Structures of the left temporal bone. CT scan (left petrous bone, axial slice) provided courtesy of Chris Danner, M.D.

POST-OP CARE & CARE FOR COMPLICATIONS

Cranial nerve and brainstem dysfunction

Facial nerve (VII): If eye closure is impaired due to VII dysfunction: ***Rx*** natural tears 2 gtts to affected eye q 2 hrs and PRN. Apply Lacrilube® to affected eye

and tape it shut q hs. If there is complete VII palsy with little chance of early recovery, or if facial sensation (Vth nerve) is also impaired, tarsorrhaphy is performed within a few days.

Facial re-animation (e.g. hypoglossal-facial anastomosis) is performed after 1-2 months if VII was divided, or if no function returns after 1 year with an anatomically intact nerve.

Vestibular nerve (VIII): Vestibular dysfunction is common post-op, nausea and vomiting due to this (and also intracranial air) is common. Balance difficulties due to this clear rapidly, however, ataxia from brainstem dysfunction may have a permanent component.

Lower cranial nerves: The combination of IX, X and XII dysfunction creates swallowing difficulties and creates a risk of aspiration.

Brainstem dysfunction: Brainstem dysfunction may occur from dissection of tumor off of the brainstem. This may produce ataxia, contralateral paresthesias in the body… Although there may be improvement, once present, there is often some permanent residual.

CSF fistula

Also, see *CSF fistula (cranial)*, page 300 for general information. CSF fistula may develop through the skin incision, the ear (CSF otorrhea) through a ruptured tympanic membrane, or via the eustachian tube and then through the nose (rhinorrhea) or down the back of the throat.

Rhinorrhea may occur through any of the following routes (circled numbers in *Figure 21-3*):

- ❶ via the apical cells to the tympanic cavity **(TC)** or eustachian tube (the most common path)
- • entry into the bony labyrinth - in order to reach the middle ear would require rupture e.g. of the oval window by overpacking bone wax into the labyrinth)
  - ❷ through the vestibule of the horizontal semicircular canal **(SCC)**
  - ❸ through the posterior SCC (the posterior SCC is the most common area that is entered by drilling)
- ❹ follows the perilabyrinthine cells and tracts to the mastoid antrum
- ❺ through the mastoid air cells at the craniotomy site

Most leaks are diagnosed within 1 week of surgery, although 1 presented 4

years post-op[258]. They appear to be more common with more lateral unroofing of the IAC[258]. Meningitis complicates a CSF leak in 5-25% of cases, and usually develops within days of the onset of leak[258]. Hydrocephalus may promote the development of a CSF fistula.

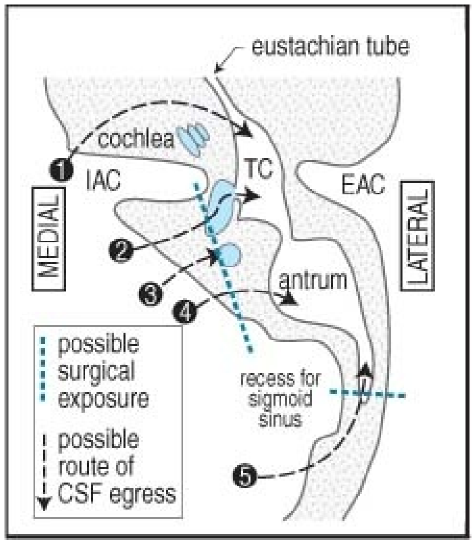

Figure 21-3 Possible routes for CSF rhinorrhea following vestibular schwannoma surgery (*see text*) (right petrous bone, axial slice). Adapted from Surgical Neurology, Vol. 43, Nutik S L, Korol H W, Cerebrospinal Fluid Leak After Acoustic Neuroma Surgery, 553-7, 1995, with permission from Elsevier Science

Treatment:[25-35]% of leaks stop spontaneously (one series reported 80%)[258]. Treatment options include:

1. non-surgical:
   A. elevate HOB
   B. if leak persists: a percutaneous lumbar subarachnoid drain may be tried[259, 260], although some debate its efficacy[255], and there is a theoretical risk of drawing bacteria into the CNS
2. surgical treatment for persistent leaks:
   A. re-explore and coat mastoid air cells with bone wax, free-muscle grafts, or fibrin glue. Rewaxing the exposed air cells fails to stop the leak in ≈ 38% of cases, but is still the procedure of choice if hearing is preserved[258] (current production methods of bone wax may result in higher leakage rates if the dural closure is not watertight than with the older formulation[261])
   B. cover bone surface with dural flap, pericranium or fascia lata
   C. when the IAC has been drilled and if the VII & VIII nerves are completely lost: pack IAC with muscle

D. if no hearing on that side (the following is usually done in collaboration with an ENT or skull-base surgeon)
   1. reuse the same incision, but stay extradural and utilize a middle-ear approach to perform a mastoidectomy and pack the area with fat[262]. Fails in 4-23% of cases[258]
   2. more aggressive treatment: fat obliteration of the eustachian tube, middle ear, and mastoid[263] (occludes drainage from apical air cells or oval window)[258]

E. if the leak occurred because of the development of hydrocephalus, adjunctive CSF shunting is usually also necessary

OUTCOME & FOLLOW-UP

Complete surgical removal was reported in 97-99% of cases[264].

SURGICAL MORBIDITY AND MORTALITY

Also see *Post-op considerations for p-fossa crani's*, page 157. Estimated frequency of some complications[265]: CSF leakage in 4-27%[258] (*see above*), meningitis in 5.7%, CVA in 0.7%, subsequent requirement for CSF shunt (for hydrocephalus or to treat leak) in 6.5%.

The mortality rate is ≈ 1% at specialized centers[241, 264, 266].

CRANIAL NERVE DYSFUNCTION

Table 21-35 shows statistics of VII and VIII cranial nerve preservation following suboccipital removal of VSs. For more details, *see below*.

Post-radiation cranial neuropathies generally appear 6-18 months following stereotactic radiosurgery **(SRS)**[268], and since more than half resolve within 3-6 months after the onset the recommendation is treat these with a course of corticosteroids.

Table 21-35 Cranial nerve preservation in retrosigmoid removal of VSs*

Size of tumor	Preserved function	
	VII nerve	VIII nerve
< 1 cm	95-100%	57%
1-2 cm	80-92%	33%
> 2 cm	50-76%	6%

* series of 135 VSs[267 (p 729)] and other sources[127 (p 3337), 264]

Facial nerve (VII)

See Table 21-27, page 622 for the House and Brackmann grading scale. Grades 1-3 are associated with acceptable function. In one surgical series, the facial nerve was preserved with all tumors ≤ 2 cm; it was preserved only in 29% of tumors > 4 cm[222]. Continuous recording of spontaneous EMG activity and responses to electrical stimulation during surgery may improve preservation of VII nerve[269, 270]. If VII is anatomically preserved, partial post-op facial weakness will usually resolve, but may take up to one year. In ≈ 13% of cases, anatomic preservation of VII is not possible.

SRS for tumors ≤ 3 cm diameter[271]: transient VII weakness occurred in 15%, and V dysfunction (usually temporary) developed in 18%. In another series[272], 92% of cases had grade 1-2 function post op (compared to 90% for microsurgery[273]). Stereotactic radiation *therapy* **(SRT)** had 2% incidence of new facial palsy[274].

Vestibulo-acoustic nerve (VIII)

Patients with unilateral VS and Class I or II hearing (see *Table 21-30*, page 623) comprised ≈ 12% of cases in a large series[275]. Preservation of hearing is critically dependent on tumor size, with little chance of preservation with tumors > 1-1.5 cm diameter. Chances of preserving hearing may possibly be improved by intraoperative brainstem auditory evoked potential monitoring[276]. In centers treating large numbers of VSs, hearing *preservation* rates of 35-71% can be achieved with tumors < 1.5 cm[275, 277] (although a range of 14-48% may be more realistic[278]). Hearing may rarely be improved post-op[279].

SRS: for tumors ≤ 3 cm diameter[271], hearing was preserved in 26% of 65 cases with pre-op pure tone threshold < 90 dB. Hearing loss has been correlated with increase in tumor size[280]. • **NB**: there is a high rate of hearing loss at 1 year. SRT: useful hearing was preserved in 93%[274].

Vestibular nerve function is rarely normal post-op. Attempts at “vestibular” sparing surgery have shown no better results than surgery not specifically addressing this issue. Most patients with unilateral loss of vestibular nerve function will learn to compensate to a significant degree with input from the contralateral side, if normal. Patients with ataxia as a result of brainstem injury from the tumor or the surgery will have more difficulties post-op. Some patients will seem to do well initially post-op with respect to vestibular nerve function, only to undergo a delayed deterioration several months post-op. These cases

likely represent aberrant regeneration of the vestibular nerve fibers and may be extremely difficult to manage. Some experts advocate cutting the vestibular nerve (as for Meniere's disease, *see page 840*).

Trigeminal nerve (V)

Postoperative trigeminal nerve symptoms occur transiently in 22% and permanently in 11% following microsurgery, similar to the results of SRS[272]. New facial numbness occurred in 2% with SRT[274].

Lower cranial nerves

Injuries to IX, X and XI occur infrequently following surgery on large tumors that distort the nerves and displace them inferiorly against the occipital bone.

Recurrence

Following microsurgery (MS)

Recurrence is highly dependent on extent of removal. However, recurrence can develop in tumors that were apparently totally removed, or when subtotal resection was performed. This can occur many years after treatment. Tumor progression rate following subtotal resection is ≈ 20%[278]. All patients should be followed with imaging (CT or MRI). In older series with up to 15 yrs follow-up, local control rate **(LCR)** after "total resection" is ≈ 94%. More recent series with MRI follow-up indicate recurrence rates of 7-11% (3-16 yrs follow-up)[278].

Use of EBRT

EBRT may improve LCR in incompletely resected tumors as shown in *Table 21-36* (note: with the long survival expected with benign tumors, post XRT complications may occur).

Table 21-36 Local control rates of surgery vs. surgery + EBRT for VSs[281]

Extent of surgical removal	Local control rate (LCR)	
	Surgery	Surgery + EBRT*
gross total	60/62 (97%)	no data
near total (90-99%)	14/15 (93%)	2/2 (100%)

subtotal (< 90%)	7/13 (54%)	17/20 (85%)*
biopsy only	no data	3/3 (100%)

* with doses < 45 Gy, LCR was 33%; with > 45 Gy LCR was 94%

Microsurgery vs. SRS

The long-term results for SRS using the current recommended dose of 14 Gy are still not known[282]. In a non-randomized retrospective study[272] of VSs < 3 cm dia, the short-term LCR (median 24 mos follow-up) was 97% for microsurgery vs. 94% for stereotactic radiosurgery **(SRS)**. However, for benign tumors, long-term followup is critical, and this study *suggests* that the long-term LCR will be better for MS than SRS. SRS studies with long-term follow-up[283] are not directly comparable because in the cases with longest follow-up, higher radiation doses were used with a resultant higher incidence of radiation complications, and an anticipated better LCR.

Initially there may be temporary enlargement of the tumor accompanied by loss of central contrast enhancement following SRS in ≈ 5% of patients[284] (with up to 2% of patients showing actual initial tumor growth), and so the need for further treatment after SRS should be postponed until there is evidence of sustained growth[285]. Surgery should be avoided during the interval from 6 to 18 months after SRS because this is time of maximum damage from the radiation[285].

Although the numbers are small, there have been indications that the rate of VII nerve injury may be higher in patients undergoing microsurgery following SRS failure[286, 287], however, this has been disputed[285]. Lastly, there is a potential for malignant trans-formation following SRS including **triton tumors**[288, 289] (malignant neoplasms with rhabdoid features) or the induction of skull base tumors (reported with external beam radiation[290]), as well as the risk of late arterial occlusion (the AICA lies near the surface of VSs), any of which may occur many years later.

Treatment for recurrence following microsurgery

Repeat surgery for recurrent VS is an option. One series of 23 patients[291] showed that 6 of 10 patients with moderate or normal VII function maintained at least moderate function after reoperation, 3 patients had increased ataxia, and 1 patient had a cerebellar hematoma. The use of SRS has been endorsed by some for recurrence of VS following one or more MS procedures[278]. Using SRS for

recurrent VSs resulted in worsening of facial nerve function in 23% of patients with Grade I-III function before SRS (median follow-up = 43 mos), and 14% developed new trigeminal symptoms[278]. 6% of patients developed tumor progression after SRS.

Hydrocephalus

May occur following treatment (MS or SRS) for VS, and may even occur years later. The increased CSF pressure may also predispose to development of a CSF fistula.

21.2.9. Pituitary tumors

Key concepts:

- most are benign adenomas arising from the anterior pituitary (adenohypophysis)
- presentation (*see below*): most commonly present due to hormonal effects (includes: hyperprolactinemia, Cushing's syndrome, acromegaly…), mass effect (most commonly: bitemporal hemianopsia from compression of optic chiasm), as an incidental finding, or infrequently with pituitary apoplexy (*see page 635*)
- work-up for a newly diagnosed intrasellar lesion: see *Table 21-40*, page 642
- treatment (*see page 649*): some prolactinomas may be treated medically (DA agonists). Other options include transsphenoidal or transcranial surgery, or XRT
- post-op concerns include: diabetes insipidus, adrenal insufficiency, CSF leak

For a review of pituitary embryology & neuroendocrinology, *see page 109*.

Pituitary adenomas

Most primary pituitary tumors are benign adenomas which arise from the anterior pituitary gland (adenohypophysis). Neurohypophyseal tumors are rare (see *Pituicytoma*, page 641). Adenomas may be classified by a number of schemes, including: by endocrine function (aided by immunostaining), by light microscopy with routine histological staining (*see page 641*), and by electron microscopic appearance.

Microadenoma: A pituitary tumor < 1 cm diameter. Currently, 50% of pituitary

tumors are < 5 mm at time of diagnosis. These may be difficult to find at the time of surgery.

Macroadenomas: Tumors > 1 cm diameter.

Pituitary carcinoma[292]

Rare (< 140 reports). Usually invasive and secretory (most common hormones: ACTH, PRL). Can metastasize, at which point prognosis is poor (66% 1-year mortality). Little improvement with further surgery, XRT, or chemotherapy.

EPIDEMIOLOGY

Pituitary tumors represent ≈ 10% of intracranial tumors (incidence is higher in autopsy series). They are most common in the 3rd and 4th decades of life, and affect both sexes equally. The incidence is increased in **multiple endocrine adenomatosis** or neoplasia (**MEA** or **MEN**)

DIFFERENTIAL DIAGNOSIS OF PITUITARY TUMORS

See page 1215 which also includes non-neoplastic etiologies.

CLINICAL PRESENTATION OF PITUITARY TUMORS

Classically, pituitary tumors are divided into functional (or secreting), and nonfunctional (AKA endocrine-inactive, which are either nonsecretory, or else secrete products such as gonadotropin that do not cause endocrinologic symptoms). Nonsecreting tumors usually do not present until of sufficient size to cause neurologic deficits by mass effect, whereas the former frequently present earlier with symptoms caused by physiologic effects of excess hormones that they secrete[293].

Presentation

Main modes: endocrine syndromes, mass effect, incidental finding, pituitary apoplexy.

1. endocrinologic disturbance:
   A. **hormone oversecretion** (secretory tumor): ≈ 65% of adenomas secrete an active hormone (48% prolactin, 10% GH, 6% ACTH, 1% TSH)[294]:
      1. prolactin **(PRL)**: can cause amenorrhea-galactorrhea syndrome in

females), impotence in males (*see page 637*). Etiologies:
   a. prolactinoma: neoplasia of pituitary lactotrophs (*see page 637*)
   b. stalk effect: pressure on the pituitary stalk may reduce the inhibitory control over PRL secretion (*see page 644*)
2. growth hormone **(GH)**: elevated GH is due to a pituitary adenoma > 95% of the time
   a. in adults: causes acromegaly (*see page 639*)
   b. in prepubertal children (before epiphyseal plate closure): produces pituitary gigantism (very rare)
3. **corticotropin** AKA adrenocorticotropic hormone **(ACTH)**:
   a. Cushing's *disease* (endogenous hypercortisolism): *see below*
   b. **Nelson syndrome**: can develop only in patients who have had an adrenalectomy (*see page 639*)
4. thyrotropin **(TSH)**: secondary (central) hyperthyroidism (*see page 640*)
5. gonadotropins (leuteinizing hormone **(LH)** and/or follicle stimulating hormone **(FSH)**): usually does not produce a clinical syndrome

B. underproduction of pituitary hormones
1. from compression of the normal pituitary by large tumors. More common with non-secretory tumors than with secretory tumors. In order of sensitivity to compression: GH, gonadotropins (LH & FSH), TSH, ACTH (mnemonic: **G**o **L**ook **F**or **T**he **A**denoma). Chronic deficiency of all pituitary hormones (panhypopituitarism) may produce pituitary cachexia (AKA Simmonds' cachexia)
   a. growth hormone deficiency[A]:
      i. in children: produces growth delay
      ii. in adults: produces vague symptoms with metabolic syndrome (decreased lean body mass, centripetal obesity, reduced exercise tolerance, impaired sense of well-being)
   b. hypogonadism: amenorrhea (women), loss of libido, infertility
   c. hypothyroidism: cold intolerance, myxedema, entrapment neuropathies (e.g. carpal tunnel syndrome), weight gain, memory disturbance, integumentary changes (dry skin, coarse hair, brittle nails), constipation, increased sleep demand
   d. hypoadrenalism: orthostatic hypotension, easy fatigability
2. ✖ NB: selective reduction of a *single* pituitary hormone is very atypical of pituitary adenomas. May occur with autoimmune

hypophysitis (*see page 1217*) which most commonly involves ACTH or ADH (causing DI[295] - *see below*))

3. **diabetes insipidus**: almost never seen pre-operatively with pituitary tumors (except possibly with pituitary apoplexy, *see below*). If DI is present, other etiologies should be sought (e.g. (*see page 1217*)) including
   a. autoimmune hypophysitis: *see page 1217*
   b. hypothalamic glioma
   c. suprasellar germ cell tumor
4. gonadotropin deficiency (hypogonadotrophic hypogonadism) with anosmia is part of Kallmann syndrome[296]

2. **mass effect** (other than compression of the pituitary). Because they tend to get to a larger size before detection, this is more common with nonfunctioning tumors. Of functional tumors, prolactinoma is the most likely to become large enough to cause mass effect (ACTH tumor is least likely). Nonspecific symptoms include headaches. Structures commonly compressed and manifestations include:
   A. optic chiasm: classically produces **bitemporal hemianopsia** (non-congruous). May also cause decreasing visual acuity
   B. involvement of third ventricle may produce obstructive hydrocephalus
   C. cavernous sinus
      1. pressure on cranial nerves contained within (III, IV, V_1, V_2, VI): ptosis, facial pain, diplopia (see *Invasive pituitary adenomas* below)
      2. occlusion of the cavernous sinus: proptosis, chemosis
      3. encasement of the carotid artery by tumor: may cause slight narrowing, but complete occlusion is rare
3. incidental finding on imaging study done for other reasons
4. pituitary apoplexy (*see below*)
5. invasive adenomas may rarely present with CSF rhinorrhea[297] (*see page 637*)
6. macroadenomas may produce H/A possibly via increased intrasellar pressure
7. seizures are rarely attributable to pituitary adenomas

A. a growth hormone stimulation test (*see page 648*) is more sensitive and specific for GH deficiency than measuring basal GH levels

PITUITARY APOPLEXY

Key concepts:

> • due to expansion of a pituitary adenoma from hemorrhage or necrosis
> • typical presentation: paroxysmal H/A with endocrinologic and/or neurologic deficit (usually ophthalmoplegia or visual loss)
> • management: immediate administration of glucocorticoids, and transsphenoidal decompression within 7 days in most cases

Definition: Neurologic and/or endocrinologic deterioration due to sudden expansion of a mass within the sella turcica.

Etiology: Sudden intrasellar expansion may occur as a result of hemorrhage, necrosis[298, 299] and/or infarction within a pituitary tumor and adjacent pituitary gland. Occasionally, hemorrhage occurs into a normal pituitary gland or Rathke's cleft cyst[300].

Clinical features of pituitary apoplexy: Patients often present with abrupt onset of H/A, visual disturbance, and loss of consciousness. Neurologic involvement includes:

1. visual disturbances: one of the most common findings. Includes:
   A. ophthalmoplegia (unilateral or bilateral): opposite the situation with a pituitary tumor, ophthalmoplegia occurs more often (78%) than visual pathway deficits (52-64%)[301]
   B. one of the typical field cuts seen in pituitary tumors (*see page 642*)
2. reduced mental status: due to ↑ ICP or hypothalamic involvement
3. cavernous sinus compression can cause venous stasis and/or pressure on any of the structures within the cavernous sinus
   A. trigeminal nerve symptoms
   B. proptosis
   C. ophthalmoplegia (Cr. N. III palsy is more common than VI)
   D. ptosis may be an early symptom[302,303]
   E. pressure on carotid artery
   F. compression of sympathetics within the cavernous sinus may produce a form of Horner's syndrome with unilateral ptosis, miosis, & anhidrosis limited to the forehead
   G. carotid artery compression may cause CVA or vasospasm
4. when hemorrhage breaks through the tumor capsule and the arachnoid

membrane into the chiasmatic cistern, signs and symptoms of SAH may be seen
   A. N/V
   B. meningismus
   C. photophobia
5. increased ICP may produce lethargy, stupor or coma
6. hypothalamic involvement may produce
   A. hypotension
   B. thermal dysautoregulation
   C. cardiac dysrhythmias
   D. respiratory pattern disturbances
   E. diabetes insipidus
   F. altered mental status: lethargy, stupor or coma
7. suprasellar expansion can produce acute hydrocephalus

Epidemiology

In Wilson's series, 3% of his patients with macroadenomas had an episode of pituitary apoplexy. In another series of 560 pituitary tumors, a high incidence of 17% was found (major attack in 7%, minor in 2%, asymptomatic in 8%)[304]. It is common for apoplexy to be the initial presentation of a pituitary tumor[305].

Evaluation

CT or MRI shows hemorrhagic mass in sella turcica and/or suprasellar region, often distorting the anterior third ventricle.

Cerebral angiography should be considered in cases where differentiating pituitary apoplexy from aneurysmal SAH is difficult.

Management of pituitary apoplexy

Pituitary function is consistently compromised, necessitating rapid administration of corticosteroids and endocrine evaluation.

In the absence of visual deficits, prolactinomas may be treated with bromocriptine.

Rapid decompression is required for: sudden constriction of visual fields, severe and/or rapid deterioration of acuity, or neurologic deterioration due to hydrocephalus. Surgery in ≤ 7 days of pituitary apoplexy resulted in better

improvement in ophthalmoplegia (100%), visual acuity (88%) and field cuts (95%) than surgery after 7 days[306]. Decompression is usually via a transsphenoidal route (transcranial approach may be advantageous in some cases). Goals of surgery:

1. to decompress the following structures if under pressure: optic apparatus, pituitary gland, cavernous sinus, third ventricle (relieving hydrocephalus)
2. obtain tissue for pathology
3. complete removal of tumor is usually not necessary
4. for hydrocephalus: ventricular drainage is generally required

INVASIVE PITUITARY ADENOMAS

About 5% of pituitary adenomas become locally invasive. The genetic make-up of these tumors may differ from more benign adenomas[308], even though the histology is similar. Numerous classifications systems have been devised, Wilson's system[307] (modified from Hardy[309, 310]) is shown in *Table 21-37*.

The clinical course is variable, with some tumors being more aggressive than others. Occasionally, these tumors grow to gigantic sizes (> 4 cm dia), and these are often very aggressive and follow a malignant course[311].

At times, an adenoma may push the medial wall of the cavernous sinus ahead of it without actually perforating this dural structure[312]. This is difficult to reliably identify on MRI, and the most definitive sign of cavernous sinus invasion is carotid artery encasement[313].

Table 21-37 Anatomic classification of pituitary adenoma (modified Hardy system)[307]

Extension
• **Suprasellar extension**
0: none
A: expanding into suprasellar cistern
B: anterior recesses of 3rd ventricle obliterated
C: floor of 3rd ventricle grossly displaced
• **Parasellar extension**
D*: intracranial (intradural)
E: into or beneath cavernous sinus (extradural)
Invasion/Spread
• **Floor of sella intact**
I: sella normal or focally expanded; tumor < 10 mm
II: sella enlarged; tumor ≥ 10 mm
• **Sphenoid extension**
III: localized perforation of sellar floor
IV: diffuse destruction of sellar floor
• **Distant spread**
V: spread via CSF or blood-borne

* specify: 1) anterior, 2) middle, or 3) posterior fossa

Presentation:

1. visual system
   A. most present due to compression of the optic apparatus, usually producing *gradual* visual deficit (however, sudden blindness is not unheard of)
   B. extraocular muscle deficits may occur with cavernous sinus invasion, and usually develop *after* visual loss
   C. exophthalmos may occur with orbital invasion due to compromise of orbital venous drainage
2. hydrocephalus: suprasellar extension may obstruct one or both foramen of Monro
3. invasion of the skull base may lead to nasal obstruction or **CSF rhinorrhea**, which occasionally may be precipitated by tumor shrinkage in response to bromocriptine[314]
4. tumors that secrete prolactin often present with findings of hyperprolactinemia (*see page 634*) and with these, the prolactin levels are usually > 1000 ng/ml (caution: giant invasive adenomas with very high PRL production may have a falsely low PRL level due to “hook effect”, *see page 644*)

HORMONALLY ACTIVE PITUITARY TUMORS

PROLACTINOMAS

The most common secretory adenoma. Arise from neoplastic transformation of anterior pituitary lactotrophs. See *Table 21-42*, page 644 for DDx of hyperprolactinemia.

Manifestations of prolonged hyperprolactinemia:

1. females: amenorrhea-galactorrhea syndrome (AKA Forbes-Albright syndrome, AKA Ahumada-del Castillo syndrome). Variants: oligomenorrhea, irregular menstrual cycles. 5% of women with primary amenorrhea will be found to have a PRL-secreting pituitary tumor[315]. Remember: pregnancy is the most common cause of secondary amenorrhea in females of reproductive potential. The galactorrhea may be spontaneous or expressive (only on squeezing the nipples)
2. males: impotence, decreased libido. Galactorrhea is rare (estrogen is also usually required). Gynecomastia is rare. Prepubertal prolactinomas may

result in small testicles and feminine body habitus

3. either sex:
   A. infertility is common
   B. bone loss (osteoporosis in women, and both cortical and trabecular osteopenia in men) due to a relative estrogen deficiency, not due to the elevated prolactin itself

At the time of diagnosis, 90% of prolactinomas in women are microadenomas, vs. 60% for males (probably due to gender specific differences in symptoms resulting in earlier presentation in females). Some tumors secrete both PRL and GH.

Cushing's disease

Cushing's *syndrome* **(CS)** is a constellation of findings caused by hypercortisolism. **Cushing's disease** (endogenous hypercortisolism due to hypersecretion of ACTH by an ACTH secreting pituitary adenoma) is one cause of CS. The most common cause of CS is iatrogenic (administration of *exogenous* steroids). Possible etiologies of endogenous hypercortisolism are shown in *Table 21-38*. To determine the etiology of CS, see *Dexamethasone suppression test* on page 646.

Prevalence of Cushing's *disease*: 40 cases/million population. ACTH-producing adenomas comprise 10-12% of pituitary adenomas[316]. Cushing's *disease* is 9 times more common in women, whereas ectopic ACTH production is 10 times more common in males. Non-iatrogenic CS is 25% as common as acromegaly.

At the time of presentation, over 50% of patients with Cushing's disease have pituitary tumors < 5 mm in diameter, which are very difficult to image with CT or MRI. Most are basophilic, some (especially the larger ones) may be chromophobic. Only ≈ 10% are large enough to produce some mass effect, which may cause enlargement of the sella turcica, visual field deficit, cranial nerve involvement and/or hypopituitarism.

Conversion factors[317] for ACTH and cortisol between U.S. units and SI units are shown in *Eq 21-1* and *Eq 21-2*.

$$\text{ACTH: } 1 \text{ pg/ml} = 1 \text{ ng/liter} \qquad \textbf{Eq 21-1}$$

$$\text{cortisol: } 1\ \mu\text{g/dl} = 27.59 \text{ nmol/liter} \qquad \textbf{Eq 21-2}$$

Table 21-38 Causes of endogenous hypercortisolism

Site of pathology	Secretion product	Percent of cases	ACTH levels
pituitary corticotroph adenoma (Cushing's *disease, see page 638*)	ACTH	60-80%	slightly elevated*
ectopic ACTH production (most are lung tumors, others: pancreas...) *see page 639*		1-10%	very elevated
adrenal (adenoma or carcinoma)	cortisol	10-20%	low
hypothalamic or ectopic secretion of corticotropin-releasing hormone (CRH) producing hyperplasia of pituitary corticotrophs (pseudo-Cushing's state) *see page 646*	CRH	rare	elevated

* ACTH may be normal or slightly elevated; normal ACTH levels in the presence of hypercortisolism are considered inappropriately elevated

Clinical findings in Cushing's disease (and also Cushing's syndrome) include:

1. weight gain
   A. generalized in 50% of cases
   B. centripetal fat deposition in 50%: trunk, upper thoracic spine ("buffalo hump"), supraclavicular fat pad, neck, "dewlap tumor" (episternal fat), with round plethoric face ("moon facies") and slender extremities
2. hypertension
3. ecchymoses and purple striae, especially on flanks, breasts and lower abdomen
4. amenorrhea in women, impotence in men, reduced libido in both
5. hyperpigmentation of skin and mucous membranes: due to MSH cross-reactivity of ACTH. Occurs only with elevated ACTH, i.e. Cushing's disease (not Cushing's syndrome) or ectopic ACTH production (also see *Nelson's syndrome (or Nelson syndrome) (NS)* below)
6. atrophic, tissue-paper thin skin with easy bruising and poor wound healing
7. psychiatric: depression, emotional lability, dementia
8. osteoporosis
9. generalized muscle wasting with complaints of easy fatigability
10. elevation of other adrenal hormones: androgens may produce hirsutism and acne
11. sepsis: associated with advanced Cushing's syndrome

Laboratory findings in Cushing's disease:

1. hyperglycemia: diabetes or glucose intolerance
2. hypokalemic alkalosis
3. loss of diurnal variation in cortisol levels

4. normal or elevated ACTH levels
5. failure to suppress cortisol with low-dose (1 mg) dexamethasone test: *see page 646*
6. elevated 24-hour urine free-cortisol
7. CRH levels will be low (not commonly measured)

Ectopic ACTH secretion

Usually secreted by tumors, most commonly small-cell carcinoma of the lung, thymoma, carcinoid tumors, pheochromocytomas, and medullary thyroid carcinoma. In addition to findings of Cushing's syndrome, patients are typically cachectic due to the malignancy which is usually rapidly fatal.

NELSON'S SYNDROME (OR NELSON SYNDROME) ***(NS)***

Key concepts:

> • a rare condition that follows 10-30% of total bilateral adrenalectomies performed for Cushing's disease
> • classic triad: hyperpigmentation (skin & mucus membranes), abnormal ↑ ACTH, and progression of pituitary tumor (the last criteria is now controversial)
> • treatment options: surgery (transsphenoidal or transcranial), XRT, medication

A rare condition that occurs in 10-30% of patients following total bilateral adrenalectomy **(TBA)** for treatment of Cushing's syndrome. NS is due to continued growth of corticotroph (ACTH-secreting) adenoma cells. Usually occurs 1-4 years after TBA (range: 2 mos-24 years)[316]. Theoretical explanation (unproven)[318]: following TBA, hypercortisolism resolves, and CRH levels increase back to normal from the (reduced) suppressed state; corticotroph adenomas in patients with NS have an increased & prolonged response to CRH resulting in increased growth. Also, corticotrophs in NS and CD show reduced inhibition by glucocorticoids. It is controversial if some cases may be related to insufficient glucocorticoid replacement after TBA[316].

Manifestations[318]

1. **hyperpigmentation** (due to melanin stimulating hormone **(MSH)** cross reactivity of ACTH and actual increased levels of MSH due to increased

propiomelanocortin production). Often the earliest sign that Nelson's syndrome is developing. Look for linea nigra (midline pigmentation from pubis to umbilicus) and hyperpigmentation of scars, gingivae, and areolae. DDx of hyperpigmentation includes: primary adrenal insufficiency (high levels of ACTH), ectopic ACTH secretion, hemochromatosis (more bronze color), jaundice (yellowish)

2. tumor growth → increased mass effect or invasion: the most serious consequence. These corticotroph tumors are among the most aggressive of pituitary tumors[319 (p 545)]. May produce any of the problems associated with macroadenomas (optic nerve compression, cavernous sinus invasion, pituitary insufficiency, H/A, bony invasion…) as well as necrosis with precipitous intracranial hypertension[320] (pituitary apoplexy, *see page 635*)
3. malignant transformation of the corticotroph tumor (very rare)
4. hypertrophy of adrenal tissue rests: may be located in the testes → painful testicular enlargement and oligospermia. Rarely the rests can secrete enough cortisol to normalize cortisol levels or even cause a recurrence of Cushing's disease despite the adrenalectomy

Laboratories & tests

1. ACTH > 200 ng/L (usually thousands of ng/L) (normal: usually < 54 ng/L)
2. exaggerated ACTH response to CRH (not required for diagnosis)
3. other pituitary hormones may be affected as with any macroadenoma causing mass effect (*see page 635*) and endocrine screening should be done (*see page 642*)
4. formal visual field testing should be done in patients with suprasellar extension or in those being considered for surgery (as a baseline) (*see page 642*).

Treatment

For treatment, *see page 650*.

Acromegaly

Key concepts:

> • abnormally high levels of growth hormone in an adult. > 95% of cases are due to a benign pituitary somatotroph adenoma, > 75% are > 10 mm at time

of diagnosis

- effects include soft tissue and skeletal changes, cardiomyopathy, colon Ca
- work-up (*page 647*): endocrine tests (*page 642*), cardiology consult, colonoscopy
- treatment (*see page 652*): surgery for most, and then if necessary, medical therapy (*page 652*) and/or XRT (*see page 656*)
- suggested criteria for biochemical cure (*page 662*): normal IGF-1, growth hormone level < 5 ng/ml, AND GH nadir of < 1 ng/ml after OGST (*see page 662*)

Incidence: 3 cases/1-million persons/year. > 95% of cases of excess GH result from a pituitary somatotroph adenoma. Growth hormone carcinoma is extremely rare. Ectopic GH secretion may occur uncommonly with: carcinoid tumor, lymphoma, pancreatic islet-cell tumor. By the time of diagnosis, > 75% of pituitary GH tumors are macroadenomas (> 10 mm dia) with cavernous sinus invasion and/or suprasellar extension.

25% of acromegalics have thyromegaly with normal thyroid studies. 25% of GH adenomas also secrete prolactin. Acromegaly occurs rarely as part of a genetic syndrome, including: multiple endocrine neoplasia type 1 (MEN 1), McCune-Albright syndrome, familial acromegaly, and Carney complex[321].

Clinical

Elevated levels of GH in children before closure of the epiphyseal plates in the long bones produces **gigantism**. Usually presents in the teen years.

In adults, elevated GH levels produces acromegaly (age: usually > 50 yrs) with findings that may include[322, 323] (also *see Table 21-39*):

1. skeletal overgrowth deformities
   A. increasing hand and foot size
   B. thickened heel pad
   C. frontal bossing
   D. prognathism
2. cardiovascular
   A. cardiac findings (structural and functional): arrhythmias, valvular disease, concentric myocardial hypertrophy
   B. hypertension (30%)
3. soft tissue swelling (includes macroglossia)
4. glucose intolerance

5. peripheral nerve entrapment syndromes (including carpal tunnel syndrome)
6. debilitating headache
7. excessive perspiration (especially palmar hyperhidrosis)
8. oily skin
9. joint pain
10. sleep apnea
11. fatigue
12. colon cancer: risk is ≈ 2 **x** risk of general population[324]

Patients with elevated levels of GH (including partially treated cases) have 2-3 times the expected mortality rate[325], primarily due to hypertension, diabetes, pulmonary infections, cancer, and cardiovascular disease (*see Table 21-39*). Soft-tissue swelling and nerve entrapment may be reversible with normalization of GH levels, however many disfiguring changes and health risks are permanent (*see Table 21-39*).

Table 21-39 Risks of long-term exposure to excess growth hormone (GH)[325]

Arthropathy

• unrelated to age of onset or GH levels
• usually with longstanding acromegaly
• reversibility*:
  • rapid symptomatic improvement
  • bone & cartilage lesions irreversible

Peripheral neuropathy

• intermittent anesthesias, paresthesias
• sensorimotor polyneuropathy
• impaired sensation
• reversibility*:
  • symptoms may improve
  • onion bulbs (whorls) do not regress

Cardiovascular disease

• cardiomyopathy
  • reduced LV diastolic function
  • increased LV mass and arrhythmias
  • fibrous hyperplasia of connective tissue
• HTN: exacerbates cardiomyopathic changes
• reversibility*: may progress even with normal GH

Respiratory disease
• upper airway obstruction: caused by soft tissue overgrowth and decreased pharyngeal muscle tone with sleep apnea in ≈ 50% • reversibility*: generally improves
Neoplasia
• increased risk of malignancies (especially colonCa) & soft-tissue polyps

• reversibility*: unknown	
Glucose intolerance	
• occurs in 25% of acromegalics (more common with family history of DM)	
• reversibility*: improves	

* reversibility with normalization of GH levels

THYROTROPIN (TSH)-SECRETING ADENOMAS

Rare: comprise ≈ 0.5-1% of pituitary tumors[294, 326]. Produces **central (secondary) hyperthyroidism**[A]: elevated circulating T_3 and T_4 levels, with elevated or inappropriately normal TSH[327] (TSH should be undetectable in primary hyperthyroidism). Up to 33% of tumors positive for TSH immunostaining are nonsecretory[327]. Many of these tumors are plurihormonal, but the secondary hormone is usually clinically silent. Most of these tumors are aggressive and invasive and are large enough at presentation to also produce mass effect (especially if prior thyroid ablative procedures have been done, which occurs in up to 60% of cases due to lack of recognition of pituitary abnormality[327, 328]).

A. NB: central hyperthyroidism may also occur with pituitary resistance to thyroid hormones[327]

Symptoms of hyperthyroidism: anxiety, palpitations (due to a-fib), heat intolerance, hyperhidrosis, and weight gain despite normal or increased intake. Signs: hyperactivity, lid lag, tachycardia, irregular rhythm when a-fib is present, hyperreflexia, tremor. Exophthalmous and infiltrative dermopathy (e.g. pretibial myxedema) are present only in Grave's disease.

PATHOLOGICAL CLASSIFICATION OF PITUITARY TUMORS

LIGHT MICROSCOPIC APPEARANCE OF ADENOMAS

In order of decreasing frequency:

- **chromophobe**: most common (ratio of chromophobe to acidophil is 4-20:1). Originally considered "non-secretory", in actuality may produce prolactin, GH, or TSH
- **acidophil** (eosinophilic): produce prolactin, TSH, or usually GH
- **basophil** → gonadotropins, ß-lipotropin, or usually ACTH → Cushing's

disease

CLASSIFICATION OF ADENOMAS BASED ON SECRETORY PRODUCTS

1. endocrine-active tumors: ≈ 70% of pituitary tumors produce 1 or 2 hormones that are measurable in the serum and cause defined clinical syndromes, these are classified based on their secretory product(s)
2. endocrine-inactive (nonfunctional) tumors[329]
   A. null-cell adenoma } constitute the bulk of endocrine-inactive adenomas
   B. oncocytoma } constitute the bulk of endocrine-inactive adenomas
   C. gonadotropin-secreting adenoma
   D. silent corticotropin-secreting adenoma
   E. glycoprotein-secreting adenoma

TUMORS OF THE NEUROHYPOPHYSIS AND INFUNDIBULUM

The most common tumors encountered in the posterior pituitary are metastases (owing to the rich blood supply).

Granular cell tumors

AKA (infundibular) granular cell tumor **(GCT)**. WHO grade I. Obsolete terms: choristoma[330], granular cell myoblastoma, pituicytoma (this term is now reserved for a circumscribed glial neoplasm - *see below*). Tumors with nests of large cells having granular, eosinophilic cytoplasm.

While rare, GCTs are the most common *primary* tumor of the neurohypophysis and pituitary stalk/infundibulum[331] with a predilection for the stalk (these result in suprasellar extension). GCTs have been identified in the gastrointestinal tract, genitourinary tract, orbital region as well as in other locations of the central nervous system with no connection to the pituitary gland or hypothalamus (e.g. spinal meninges[332]). Female:male ratio ≥ 2:1. Asymptomatic microscopic clusters of granular cells (tumorettes) are more common, with an incidence up to 17%[333].

The most common presentation is with visual field deficits due to optic chiasm compression[330]. However, any symptom typical of a hormonally inactive sellar mass may occur.

Imaging: may appear radiographically identical to adenomas. Rarely considered in the differential diagnosis pre-op. Isodense on CT and isointense on T1WI MRI, dense homogeneous enhancement on CT & MRI.

Treatment: if GCT is suspected pre-op, a transcranial approach is preferred over transsphenoidal because of the vascularity which has prevented total resection in 60-70% of reported cases[334]. XRT may be considered for subtotal resection[331].

Pituicytoma

Less favored alternate terms include posterior pituitary astrocytoma. Rare (mostly case reports). Circumscribed tumor with spindle cells, arising from the neurohypophysis or infundibulum[335]. WHO grade I. Reported only in adults.

Treatment: surgical excision. Subtotal removal may be followed by recurrence over several years.

EVALUATION

HISTORY AND PHYSICAL

Directed to look for signs and symptoms of:

1. endocrine hyperfunction (see *Functional pituitary tumors* above), including:
   A. prolactin: amenorrhea (women), nipple discharge (primarily in women since estrogen is also required), impotence (males),
   B. thyroid: heat intolerance
   C. growth hormone: change in ring size or shoe size or coarsening of facial features, gigantism (children)
   D. cortisol: hyperpigmentation, Cushingoid features
2. endocrine deficits (due to mass effect on pituitary) (*see page 635*)
3. visual field deficit: bedside confrontational testing to rule-out visual field deficit (classically bitemporal hemianopsia, *see below*)
4. deficits of cranial nerves within cavernous sinus (III, IV, V_1, V_2, VI)

DIAGNOSTIC TESTS

Initial tests to work-up a patient presenting with a known or suspected pituitary mass are shown in *Table 21-40*. Further testing is indicated for abnormal results or for strong suspicion of specific syndromes (see indicated page for details).

Table 21-40 Summary of initial (screening) work-up for pituitary tumors

	Evaluation	Rationale	Page
	✔ Formal visual fields (usually Humphrey visual fields (**HVF**))	• compression of optic chiasm → visual field deficit (usually bitemporal hemianopsia)	*see below*
Endocrine screening	✔ 8 A.M. cortisol* & 24-hour urine free cortisol*	• cortisol ↑ in hypercortisolism (Cushing's syndrome) • cortisol ↓ in hypoadrenalism (primary or secondary)	643 and 646
Endocrine screening	✔ free T_4‡, TSH ‡ (alternatively, total T_4 may be used, if preferred)	**Hypothyroidism** • T_4 ↓ & TSH ↑ in primary hypothyroidism (this may cause thyrotroph hyperplasia in pituitary gland, *see page 645*) • T_4 ↓ & TSH nl or ↓ in secondary hypothyroidism **Hyperthyroidism (thyrotoxicosis)** • T_4 ↑ & TSH ↓ in primary hyperthyroidism • T_4 ↑ & TSH ↑ in TSH-secreting pituitary adenomas	645
Endocrine screening	✔ prolactin	• ↑ or ↑↑ with prolactinoma	643
Endocrine screening		• slight ↑ with stalk effect (usually < 90 ng/ml)	644
Endocrine screening	✔ gonadotropins (FSH, LH) and sex steroids (♀: estradiol, ♂: testosterone)	• ↓ in hypogonadotrophic hypogonadism (from mass effect causing compression of the pituitary gland) • ↑ with gonadotropin secreting adenoma	645
Endocrine screening	✔ insulin-like growth factor-1 (IGF-1) AKA somatomedin-C†	• ↑ in acromegaly • ↓ in hypopituitarism (one of the most sensitive markers)	647
Endocrine screening	✔ fasting blood glucose	↓ in hypoadrenalism (primary or secondary)	647
	✔ Radiographic studies. Either: • MRI without & with enhancement (test of choice), *or* if contraindicated • CT without & with enhancement (with coronal reconstruction) + cerebral angiogram		648

* 8 A.M. cortisol is the best test for hypocortisolism (e.g. to look for pituitary insufficiency),24-hour urine free cortisol is the best test for hypercortisolism[336] (*see page 643*) (e.g. to look for Cushing's syndrome)

† IGF-1 is the primary test for excess growth hormone (GH); direct measurement of GH is unreliable

VISUAL FIELDS

Formal visual field testing: by perimetry with a tangent screen (using the small red stimulus since desaturation of color is an early sign of chiasmal compression) or by Goldman or automated Humphrey perimeter (the latter requires good cooperation from the patient to be valid).

Visual field deficit patterns

Depends in part on location of chiasm with respect to sella turcica: the chiasm is located above the sella in 79%, posterior to the sella turcica (**postfixed** chiasm) in 4%; in front of the sella (pre-fixed) in 5%[337] (p 2135)

1. compression of the optic chiasm:
   A. **bitemporal hemianopsia** that obeys the vertical meridian: classic visual field deficit associated with a pituitary tumor. Due to impingement on crossing nasal fibers in the chiasm (*see page 829*)
   B. other reported patterns that occur rarely: monocular temporal hemianopsia

2. optic nerve compression: more likely in patients with a postfixed chiasm
   A. loss of vision in the ipsilateral eye. If carefully sought, there is usually a superior outer (temporal) quadrantanopsia in the contralateral eye[337 (p 2135)] (so-called **junctional scotoma** AKA "pie in the sky" defect) from compression of the anterior knee of Wilbrand (*see page 1071*) (may also be an early finding even without a post-fixed chiasm)
   B. may produce central scotoma or monocular reduction in visual acuity
3. compression of the optic tract: may occur with a pre-fixed chiasm. Produces **homonymous hemianopsia**

ENDOCRINOLOGIC EVALUATION

BASELINE ENDOCRINE EVALUATION (modified[338])

Also, *see Table 21-40*. May give indication of tumor type, determines whether any hormones need to be replaced, and serves as a baseline for comparison following treatment. Includes clinical assessment for signs and symptoms, as well as laboratory tests. Screening tests should be checked in all patients with pituitary tumors. Note: selective loss of a single pituitary hormone together with thickening of the pituitary stalk is strongly suggestive of autoimmune hypophysitis (*see page 1217*).

1. adrenal axis screening (for tests to assess cortisol reserve, *see page 647*):
   A. 8 AM cortisol level: better for hypocortisolism[336]. Normal: 6-18 µg/100 ml. Note: AM cortisol may normally be slightly elevated
   B. in questionable cases, including to distinguish pseudo-Cushing states from Cushing's syndrome, *see page 646*
   C. 24-hour urine free cortisol: more accurate for hypercortisolism[336] (almost 100% sensitive and specific, false negative rare except in stress or chronic alcoholism). If not elevated several times above normal, at least 2 additional determinations should be made[339]
2. **prolactin levels (PRL)**: *see page 111* for prolactin neurophysiology
   A. interpretation is shown in *Table 21-41*. *See Table 21-42* for differential diagnosis of hyperprolactinemia. Prolactin level correlates with size of prolactinomas[343]: if PRL is < 200 ng/ml, ≈ 80% of tumors are microadenomas, and 76% of these will have normal PRL after surgery; if PRL > 200, only ≈ 20% are microadenomas
   B. blood samples should be obtained midmorning (i.e. not soon after awakening) and not after stress, breast stimulation, or physical

examination, which may increase PRL levels

C. be aware of the following when interpreting PRL levels:

- because of variations in secretion (daily fluctuations can be as high as 30%) and intrinsic inaccuracies of radioimmunoassay, PRL levels should be rechecked if there is a reason to question a specific result
- heterophilic antibodies (seen in individuals routinely exposed to animal serum products) can cause anomalous results
- **stalk effect**: PRL is the only pituitary hormone primarily under inhibitory regulation (*see page 111*). Injury to the hypothalamus or pituitary stalk can cause modest elevation of PRL due to decrease in prolactin inhibitory factor **(PRIF)**. Rule of thumb: the percent chance of an elevated PRL being due to a prolactinoma is equal to one half the PRL level. Persistent post-op PRL elevation may occur even with total tumor removal as a result of injury to stalk (usually ≤ 90 ng/ml; stalk effect doubtful if PRL > 150). For stalk effect, follow these patients, do not use bromocriptine
- **"prolactin level > 200 ng/ml"**: if the lab re-ports the prolactin level as "> 200" (or some other high value) instead of an actual number, it usually indicates a very high prolactin level that exceeds the upper limits of the assay. Call the lab and ask them to determine the actual value. This usually requires serial dilutions until the PRL is in a range that their assay can quantify. The reasons this is important:
    1. treatment decisions: PRL > 500 usually indicates that surgery alone will not be able to normalize the PRL (*see page 651*)
    2. to assess response: it is essential to know what value you are starting with to determine response to therapy (medication, surgery, XRT…)
- **hook effect**: extremely high PRL levels may overwhelm the assay and produce falsely low results. Therefore, for large adenomas with a normal PRL level, have the lab perform several dilutions of the serum sample and re-run the PRL, especially in patients with clinical hyperprolactinemia
- **macroprolactinemia**: a situation where prolactin molecules polymerize and bind to immunoglobulins. Prolactin in this form has reduced biologically activity but produces a laboratory finding of hyperprolactinemia. Clinical significance is controversial[347], asymptomatic patients usually do not require treatment

3. thyroid axis: the basis for thyroid screening is shown in *Table 21-43*
   A. screening: T_4 level (total or free), thyroid-stimulating hormone **(TSH)** (AKA thyrotropin). Normal values: free T_4 index is 0.8-1.5, TSH 0.4-5.5 µU/ml, total T_4 4-12 µg/100ml (NB: be sure to check both T_4 AND TSH)
   B. further testing: thyrotropin-releasing hormone **(TRH)** stimulation test (indicated if T_4 is low or borderline): check baseline TSH, give 500 µg TRH IV, check TSH at 30 & 60 mins. Normal response: peak TSH twice baseline value at 30 mins. Impaired response with a low T_4 indicates pituitary deficiency. Exaggerated response suggests primary hypothyroidism
4. growth hormone:
   A. IGF-1 (somatomedin-C) level (*see page 647*) is the recommended initial test (testing for elevated IGF-1 is extremely sensitive for acromegaly)
   B. checking a single random GH level may not be a reliable indicator and is therefore not recommended (*see page 648*)
5. gonadal axis
   A. screening:
      1. serum gonadotropins: FSH & LH
      2. sex steroids
         a. estradiol in women
         b. testosterone in men: measure total testosterone
   B. further testing: none dependable in differentiating pituitary from hypothalamic disorders
6. neurohypophysis (posterior pituitary): deficits are rare with pituitary tumors
   A. screening: check adequacy of ADH by demonstrating concentration of urine with water deprivation (*see page 17*)
   B. further testing: measurement of serum ADH in response to infusion of hypertonic saline

Table 21-41 Significance of prolactin levels*

PRL (ng/ml)	Interpretation	Situations observed in
3-30†	normal	non-pregnant female
10-400		pregnancy (*see Table 21-42*)

2-20		postmenopausal female
25[†]-150	moderate elevation	• prolactinoma • “stalk effect” (*see text*) • other causes[§]
> 150[‡]	significant elevation	prolactinoma[§]

* Note: ectopic sites of prolactin secretion have rarely been reported (e.g. in a teratoma[344])

† normal values vary, use your lab’s reference range

‡ some authors recommend 200 ng/ml as the cutoff for probable prolactinomas[345]

§ for DDx of hyperprolactinemia see Table 21-42

Table 21-42 Differential diagnosis of elevated prolactin (PRL) level (hyperprolactinemia)*

1. pregnancy-related
   A. during pregnancy[†]: 10-400 ng/ml
   B. postpartum: PRL decreases ≈ 50% (to ≈ 100 ng/ml) in the first week postpartum, and is usually back to normal in 3 weeks
   C. in the lactating female: suckling increases PRL, which is critical for lactogenesis (once initiated, nonpregnant PRL levels can maintain lactation). First 2-3 months postpartum: basal PRL = 40-50 ng/ml, suckling → increases **x** 10-20. 3-6 months postpartum: basal PRL levels become normal or slightly elevated, and double with suckling. PRL should normalize by 6 months after weaning
2. pituitary adenoma
   A. prolactinoma: larger prolactin <u>micro</u>adenomas and macroadenomas usually produce PRL > 100 ng/ml
   B. stalk effect: rule of thumb, the percent chance of an elevated PRL being due to a prolactinoma is equal to one half the PRL level (*see page 644*)
   C. some tumors secrete both PRL and GH
3. drugs: dopamine receptor antagonists (e.g. phenothiazines, metoclopramide), oral contraceptives (estrogens), tricyclic antidepressants, verapamil, H2 antagonists (e.g. ranitidine), some SSRIs in particular paroxetine (Paxil®)[346]…
4. primary hypothyroidism: TRH (a prolactin releasing factor (PRF)) will be elevated (*see page 111*)
5. empty sella syndrome: *see page 719*
6. post-ictal: PRL usually normalizes within 1-2 hrs after a seizure (*see page 401*)
7. breast or chest-wall trauma/surgery: usually ≤ 50 ng/ml
8. excessive exercise: usually ≤ 50 ng/ml
9. stress: in some cases the stress of having the blood test is enough to elevate PRL, anorexia nervosa
10. ectopic secretion: reported in renal cell or hepatocellular tumors, uterine fibroids, lymphomas
11. infiltrating hypothalamic tumors
12. renal failure
13. cirrhosis
14. macroprolactinemia: *see text*

* hyperprolactinemia from causes other than prolactinomas rarely exceeds 200 ng/ml

† always R/O pregnancy as a cause of amenorrhea & hyerprolactinemia in a female with reproductive potential

Table 21-43 Basis for thyroid screening

Primary hypothyroidism* (problem with thyroid gland itself)	T_4	TSH
• chronic primary hypothyroidism may produce secondary pituitary hyperplasia (pituitary pseudotumor) indistinguishable from adenoma on CT or MRI. Must be considered in any patient with a pituitary mass[340, 341] • pathophysiology: loss of negative feedback from thyroid hormones causes increased TRH release from the hypothalamus producing secondary hyperplasia of thyrotrophic cells in the adenohypophysis (thyrotroph hyperplasia). The patient may present due to pituitary enlargement (visual symptoms, elevated PRL from stalk effect, enlarged sella turcica on x-rays…) • chronic stimulation from elevated TRH may rarely produce thyrotroph adenomas • labs: T_4 low or normal, TSH elevated (> 90-100 in patients presenting with thyrotroph hyperplasia), prolonged and elevated TSH response to TRH stimulation test (*see text*)	↓	↑
Secondary hypothyroidism* (insufficient TSH stimulation of thyroid)	↓	**↓ or nl**
• pituitary hypothyroidism accounts for only ≈ 2-4% of all hypothyroid cases[342] • ≈ 23% of patients with chromophobe adenomas develop secondary hypothyroidism if untreated (pituitary compression causes reduced TSH) • labs: T_4 low, TSH low or normal, reduced response to TRH stimulation test (*see text*)		
Primary hyperthyroidism (problem with thyroid gland itself)	↑	↓
• etiologies: localized hyperactive thyroid nodule, circulating antibody that stimulates the thyroid, or diffuse thyroid hyperplasia (Graves' disease, AKA ophthalmic hyperthyroidism) • labs: T_4 elevated, TSH subnormal (usually <u>undetectable</u>)		
Secondary hyperthyroidism (central hyperthyroidism)	↑	**↑ or nl**

• etiologies
  • TSH-secreting pituitary adenoma (rare)
  • pituitary resistance to thyroid hormones (disrupts negative feedback loop)
• labs: T_4 elevated, TSH elevated or inappropriately normal		

* ✖ Caution: replacing thyroid hormone with inadequate cortisol reserves (as may occur in panhypopituitarism) can precipitate adrenal crisis) (see page 650 for management)

SPECIALIZED ENDOCRINOLOGIC TESTS

Cushing's syndrome

A. tests to determine if <u>hypercortisolism</u> (Cushing's syndrome, **(CS)**) is present or not, regardless of etiology if the screening 24-hr urine free cortisol (*see page 643*) is equivocal (the basis of these tests is shown in *Table 21-44*)
   1. overnight <u>low-dose</u> dexamethasone **(DMZ)** suppression tests[348]:
      A. overnight low dose test: give DMZ 1 mg PO @ 11 P.M. and draw serum cortisol the next day at 8 A.M. Results:
         1. cortisol **< 1.8 μg/dl**[A]: Cushing's syndrome is ruled out (except for a few patients with CS who suppress at low DMZ doses, possibly due to low DMZ clearance[349])
         2. cortisol 1.8 -10 μg/dl: indeterminate, retesting is necessary
         3. cortisol > 10 μg/dl: CS is probably present. False positives can

occur in the so-called **pseudo-Cushing's state** where ectopic CRH secretion produces hyperplasia of pituitary corticotrophs that is clinically indistinguishable from pituitary ACTH producing tumors (requires further testing[349]). Seen in: 15% of obese patients, in 25% of hospitalized and chronically ill patients, in high estrogen states, in uremia, and in depression. The combined DMZ-CRH test can be used to identify this (see reference[349]). False positives also may occur in alcoholics or patients on phenobarbital or phenytoin due increased metabolism of DMZ caused by induced hepatic microsomal degradation

B. 2 day low dose test (used when overnight test is equivocal): give DMZ 0.5 mg PO q 6 hrs for 2 days starting at 6 A.M.; 24 hr urine collections are obtained prior to test and on the 2nd day of DMZ administration. Normal patients suppress urinary 17-hydroxycorticosteroids **(OHCS)** to less than 4 mg/24 hrs, whereas ≈ 95% of patients with CS have abnormal response (higher amounts in urine)[349]

2. 11 PM salivary cortisol: this is the time of the usual cortisol nadir. Test must be run at NIH approved lab. Accuracy is as good as low-dose DMZ suppression test

B. tests to distinguish primary Cushing's disease **(CD)** (*pituitary* ACTH hypersecretion) from ectopic ACTH production and adrenal tumors (40% of CD patients have normal MRI[336])

1. random serum ACTH: if **< 5 ng/L** indicates ACTH independent CS (e.g. adrenal tumor). Not sensitive or specific due to variability of ACTH levels
2. abdominal CT: usually shows unilateral adrenal mass with adrenal tumors, or normal or bilateral adrenal enlargement in ACTH-dependent cases
3. <u>high-dose</u> dexamethasone **(DMZ)** suppression test: (NB: up to 20% of patient's with CD do not suppress with high-dose DMZ. Phenytoin may also interfere with high-dose DMZ suppression[350])
   A. overnight high-dose test: obtain a baseline 8 A.M. plasma cortisol level
   B. then give DMZ 8 mg PO @ 11 P.M. and measure plasma cortisol level the next morning at 8 A.M.
   C. in 95% of CD cases plasma cortisol levels are reduced to < 50% of baseline, whereas in ectopic ACTH or adrenal tumors it will usually be unchanged
4. **metyrapone** (Metopirone®) test: performed on an inpatient basis. Give

750 mg metyrapone (suppresses cortisol synthesis) PO q 4 hrs for 6 doses. Most patients with CD will have a rise in 17-OHCS in urine of 70% above baseline, or an increase in serum 11-deoxycortisol 400-fold above baseline

5. corticotropin-releasing hormone **(CRH)** stimulation test: CD responds to exogenous CRH 0.1 µg/kg IV bolus with even further increased plasma ACTH and cortisol levels; ectopic ACTH and adrenal tumors do not[351]
6. inferior petrosal sinus **(IPS)** sampling (or, cavernous sinus sampling is preferred by some): done by interventional neuroradiologist. Uses a microcatheter to measure ACTH levels on each side at baseline, and then at 2, 5 & 10 minutes after stimulation with IV CRH (with simultaneous peripheral ACTH levels at each interval). General information:
   A. IPS sampling is not needed when the following criteria of CD are met[317]:
      1. ACTH-dependent Cushing's disease
      2. suppression with high-dose dexamethasone test (*see above*)
      3. visible pituitary adenoma on MRI
   B. may also determine likely side of a microadenoma within the pituitary (thus may be able to avoid bilateral adrenalectomy which requires lifelong gluco- and mineralo-corticoid replacement and risks Nelson's syndrome in 10-30% - *see page 639*). 15-30%[336] of the time this test falsely lateralizes the tumor due to the communication through the circular sinus
   C. a baseline IPS ACTH to peripheral ACTH ratio > 1.4:1 is consistent with primary Cushing's disease
   D. a post CRH ratio > 3 is also consistent with primary Cushing's disease
   E. complication rate: 1-2%, includes puncture of the sinus wall

A. this is the currently accepted normal value; previously it was 5 µg/dl

Table 21-44 Basis for biochemical tests in Cushing's syndrome (CS)

- normally, low DMZ doses suppress ACTH release through negative feedback on hypothalamic-pituitary axis, reducing urine and serum corticosteroids
- in ≥ 98% of cases of Cushing's syndrome, suppression occurs, but at a much higher threshold
- adrenal tumors and most (85-90%) cases of ectopic ACTH production (especially bronchial Ca) will not suppress even with high dose DMZ
- ACTH response to CRH is exaggerated in CS

• DMZ does not interfere with measurement of urinary and plasma cortisol and 17-hydroxycorticosteroids

To check cortisol reserve:

1. **cosyntropin stimulation test** 352:
   A. draw a baseline cortisol level (fasting is not required; test can be performed at any time of day)
   B. give cosyntropin (Cortrosyn®) (a potent ACTH analogue) 1 ampoule (250 mcg) IM or IV
   C. then check cortisol levels at 30 mins (optional) and at 60 mins
   D. normal response: **peak cortisol level > 18 µg/dl** AND an increment > 7 µg/dl, or a peak > 20 µg/dl regardless of the increment
   E. subnormal response: indicates **adrenal insufficiency**. In primary adrenal insufficiency, pituitary ACTH secretion will be elevated. In secondary adrenal insufficiency, *chronically* reduced ACTH causes adrenal atrophy and unresponsiveness to acute stimulation with this exogenous ACTH analogue
   F. normal response: rules out primary and overt secondary adrenal insufficiency, but may be normal in mild cases of reduced pituitary ACTH or early after pituitary surgery where adrenal atrophy has not occurred. In these cases further testing may be positive: see metyrapone test (*page 661*) or ITT (*see below*)
2. **insulin tolerance test (ITT)**: "gold standard" for assessing integrity of the hypothalamic-pituitary-adrenal axis. Cumbersome to do. Abnormal in 80% of CS. Assesses ACTH, cortisol & GH reserve
   A. rationale: an appropriate cortisol increment in response to insulin-induced hypoglycemia suggests patient will also be able to respond to other stresses (acute illness, surgery…)
   B. contraindications: seizure disorder, ischemic cardiac disease, untreated hypothyroidism
   C. pre-test preparation: D/C estrogen replacement for 6 weeks prior to test. Have 50 ml of D50 and 100 mg IV hydrocortisone available during test
   D. protocol: give regular insulin 0.1 U/kg IV push, and draw blood for glucose, cortisol and GH at 0, 10, 20, 30, 45, 60, 90 and 120 mins (monitor blood sugar by fingerstick during test, and give IV glucose if patient becomes symptomatic). If fingerstick blood sugar is not < 50 mg/dl by 30 minutes and patient is asymptomatic, give additional regular insulin 5 U IVP. There must be 2 specimens after adequate

hypoglycemia

E. results:
  1. if adequate hypoglycemia (< 40 mg/dl) was not accomplished: cortisol or GH deficiency cannot be diagnosed
  2. normal: cortisol increment > 6 µg/dl to a peak > 20
  3. peak cortisol = 16-20: steroids needed only for stress
  4. peak cortisol < 16: glucocorticoid replacement needed
  5. Cushing syndrome: increment < 6

Acromegaly

For suspected acromegaly, the most useful test is an IGF-1 level.

1. insulin-like growth factor-1 **(IGF-1)** (formerly somatomedin-C) level: an excellent integrative marker of average GH secretion. Normal levels depend on age (peaking during puberty), gender, pubertal stage and lab. Typical fasting levels by age are shown in *Table 21-45*. Estrogen may suppress IGF-1 levels
2. **growth hormone (GH)**: normal basal fasting level is < 5 ng/ml. In patients with acromegaly, GH is usually > 10 ng/ml but can be normal. Normal basal levels do not reliably distinguish normal patient from GH deficiency[353]. Furthermore, due to pulsatile secretion of GH, normal patients may have sporadic peaks up to 50 ng/ml[322]. Occasionally acromegaly may be present even with GH levels as low as 37 pg/ml[354]. ∴ random GH levels are not generally useful for *diagnosing* acromegaly (*see above* for IGF-1)
3. other tests used uncommonly
   A. oral glucose suppression test **(OGST)**: less precise and more expensive than measuring IGF-1, however may be more useful than IGF-1 for monitoring initial response to therapy. GH levels are measured at 0, 30, 60, 90 & 120 minutes after a 75 gm oral glucose load. If the GH nadir is not < 1 ng/ml, the patient is acromegalic[321, 323]. GH suppression may also be absent with liver disease, uncontrolled DM & renal failure. ✖ Relatively contraindicated in patients with DM and high glucose levels
   B. growth-hormone releasing hormone **(GHRH)** levels: may help diagnose ectopic GH secretion in a patient with proven acromegaly with no evidence of pituitary tumor on imaging. If an extrapituitary source is suspected, chest and abdominal CT and/or MRI should also

be obtained[355]

C. GHRH stimulation test: results may be discordant in up to 50% of patients with acromegaly[321] and is thus rarely used (as of this writing, pharmaceutical production of GHRF has been discontinued)

4. octreotide scan: SPECT imaging 4 and 24 hours after injection with 6.5 mCi of indium-111 Octreo-Scan, a somatostatin receptor imaging agent

Table 21-45 Normal IGF-1 by age

Age (yrs)	Level (ng/ml)
1-5	49-327
6-8	52-345
9-11	74-551
12-15	143-996
16-20	141-903
21-39	109-358
40-54	87-267
>54	55-225

RADIOGRAPHIC EVALUATION

Requires either CT or MRI. MRI has an advantage in large tumors and when evaluating for recurrence. A lateral skull x-ray may help define anatomy of sphenoid sinus in cases where transsphenoidal surgery is contemplated. ≈ 50% of pituitary tumors causing Cushing's syndrome are too small to be imaged on CT or MRI (therefore endocrinologic testing is required to prove the pituitary origin). *See page 1215* for differential diagnosis of intrasellar lesions (some are indistinguishable radiographically).

Normal AP diameter of pituitary gland: female of childbearing age (≈ 13-35 yrs)[A]: ≤ 11 mm, for all others normal is ≤ 9 mm.

A. pituitary glands in adolescent girls may be physiologically enlarged (mean height: 8.2 ± 1.4 mm) as a result of hormonal stimulation of puberty[356]

MRI

Imaging test of choice for pituitary tumors. Gives information about invasion

of cavernous sinus, and about location and/or involvement of para-sellar carotids. MRI may fail to demonstrate tumor in 25-45% of cases of Cushing's disease[357]. 3T vs. 1.5T MRI: based on 5 cases of Cushing's disease, a 3T MRI showed the adenoma more clearly in 2 cases, in 1 case it showed the tumor on the correct side opposite to where the 1.5T MRI showed it, and in 2 cases neither 1.5T nor 3T MRI could show the microadenoma)[358].

Microadenoma: 75% are low signal on T1WI, and high signal on T2WI (but 25% can behave in any way, including completely opposite to above). Enhancement is time-dependent. Imaging must be done with 5 minutes of contrast administration to see a discrete microadenoma. Initially, gadolinium enhances the normal pituitary (no blood brain barrier) but <u>not</u> the pituitary tumor. After ≈ 30 minutes, the tumor enhances about the same. Dynamic MRI scans have been used to increase the sensitivity (contrast is injected while the MRI scanner is running).

Neurohypophysis: normally is high signal on T1WI[359] (possibly due to phospholipids). Absence of this "**bright spot**" often correlates with diabetes insipidus as may occur with autoimmune hypophysitis (*see page 1217*).

Deviation of the pituitary stalk may also indicate the presence of a microadenoma. Normal thickness of the pituitary stalk is approximately equal to basilar artery diameter. Thickening of stalk is usually NOT adenoma, differential diagnosis here: lymphoma, autoimmune hypophysitis (*see page 1217*), granulomatous disease, hypothalamic glioma.

CT

Generally superseded by MRI. May be appropriate when MRI is contraindicated (e.g. pacemaker). When done, should include direct coronal imaging, or coronal reconstructions from thin-cut axial CT. If MRI cannot be done, consider also cerebral angiography to demonstrate parasellar carotid arteries and to R/O aneurysm as a possibility.

Calcium in pituitary usually signifies hemorrhage or infarction within tumor.

Enhancement (with IV contrast):

1. normal pituitary enhances densely (no BBB)
2. macroadenomas enhance more than normal pituitary
3. microadenomas enhance less (may just be slower). Diagnostic criteria:
    A. must have attenuation change on CT PLUS
    B. 2 or more of the following:
        1. focal bone erosion of sella turcica

2. focal superior bulge of gland
3. displacement of stalk (this is unreliable, and may actually deviate to opposite side)

ANGIOGRAPHY

Sometimes used in cases considered for transsphenoidal surgery (e.g. as a complement to CT) to localize the parasellar carotids (note: MRI provides this information, and evaluates involvement of cavernous sinuses, usually obviating the need for angiography).

MANAGEMENT/TREATMENT

See page 635 for treatment of pituitary apoplexy. For large invasive adenomas, *see below*. Prolactinoma is the only pituitary tumor for which medical therapy (dopamine agonist) is the primary treatment modality (in certain cases).

HORMONALLY INACTIVE MACROADENOMAS - MANAGEMENT

Due to poor response rates to medication, when treatment is indicated, surgery and/or XRT are usually the initial treatment of choice (*see below* for XRT).

MEDICAL MANAGEMENT

Non-secreting adenomas

Bromocriptine has been tried with mild reductions in tumor size in only ≈ 20% of patients. The poor results are probably due to the paucity of dopaminergic receptors on cell membranes in these tumors. Octreotide reduces tumor volume in ≈ 10% of cases. These agents have been used pre-op in some cases to decrease tumor size for surgery.

Follow-up: For asymptomatic microadenomas (< 1 cm dia), recommend: F/U pituitary MRI at years 1, 2, 5 and ± 10 (can stop F/U after 10 and possibly 5 years if no growth).

For tumors ≥ 1 cm, recommend: check visual fields, pituitary bloodwork (to R/O pituitary insufficiency) and pituitary MRI at years 0.5, 1, 2 & 5, and any time symptoms develop.

Gonadotropin-secreting tumors

Rarely, a non-functional tumor may secrete gonadotropins (FSH, LH). This does not produce a clinical syndrome. Normal and neoplastic pituitary gonadotrophs have gonadotropin-releasing hormone **(GnRH)** receptors, and may respond to long-acting GnRH agonists (by down-regulating receptors) or GnRH antagonists, but significant reductions in tumor size does not occur.

SURGICAL MANAGEMENT

Surgical indications for hormonally inactive pituitary macroadenomas:

1. tumors causing symptoms by mass effect: visual field deficit (classically: bitemporal hemianopsia, panhypopituitarism
2. some surgeons recommend surgery for macroadenomas that elevate the chiasm even in the absence of endocrine abnormalities or visual field deficit because of the possibility of injury to the optic apparatus (*see below* for invasive pituitary macroadenomas)
3. acute and rapid visual or other neurologic deterioration. May represent ischemia of the chiasm, or tumor hemorrhage/infarction causing expansion (pituitary apoplexy). The major danger is blindness (hypopituitarism can be treated with replacement therapy). Visual loss usually requires emergent decompression. Some surgeons feel that a transcranial approach is necessary, but transsphenoidal decompression is usually satisfactory[311, 329]
4. to obtain tissue for pathological diagnosis in questionable cases
5. Nelson's syndrome (*see page 639*):
   A. surgery (transsphenoidal or transcranial): the primary treatment. The aggressiveness of the tumor sometimes requires total hypophysectomy
   B. XRT (possibly SRS) is used following subtotal excision
   C. medical therapy is usually ineffective. Agents that could be considered include[316]: dopamine agonists, valproic acid, somatostatin analogues, rosiglitazone, and serotonin agonists

MANAGEMENT OF LARGE, INVASIVE ADENOMAS[311]

1. prolactinomas
   A. dopamine agonists **(DA)** (*see page 651*) unless there is unstable deficit
   B. for unstable deficit, or if the tumor does not respond to DAs: debulk the tumor transsphenoidally and then rechallenge with DA therapy

2. tumors secreting growth hormone or ACTH: an aggressive surgical approach is indicated with these tumors since the secretion product is harmful and effective medical adjuvants are lacking
   A. pre-treat invasive GH-secreting tumors with somatostatin analogue therapy before surgery to reduce surgical risks (general and cardiac)
   B. elderly patients or tumors > 4 cm diameter: debulk tumor transsphenoidally and/or adjuvant therapy (XRT and/or medications)
   C. young age and size < 4 cm: radical surgery (may be curative)
3. nonfunctional adenomas:
   A. elderly patient: expectant management is an option, with intervention for signs of progression (radiographic or neurologic)
   B. central tumor or elderly patient with progression: transsphenoidal debulking and/or XRT (residual tumor in the region of the cavernous sinus may show little or no change over several years, and with these nonfunctional tumors, there is less harm in following them than if there is a harmful secretion product)
   C. parasellar tumor and/or young age: radical surgery (often not curative)

HORMONE REPLACEMENT THERAPY (HRT)

Critical issues:

1. corticosteroids
   A. indications: inadequate cortisol reserve as demonstrate by failing a cosyntropin stimulation test (failure to achieve a peak cortisol level > 18 µg/dl in response to cosyntropin (*see page 647*))
   B. may start cortisol immediately after bloodwork for cosyntropin test is drawn (do not need to wait for test results) - then, when test results available, continue therapy based on test results
   C. ***Rx*** physiologic replacement dose: cortisol 20 mg po q AM and 10 mg po q 4 PM. Stress doses may be needed in some situations (*see page 32*)
2. thyroid hormone replacement
   A. ✖ can precipitate adrenal crisis if started before cortisol in a patient with adrenal insufficiency (as may occur in panhypopituitarism) (*see page 34*)
      1. ∴ do a cosyntropin stimulation test (*see page 647*) and start cortisol
      2. thyroid replacement may be initiated after 1 full day of cortisol. ***Rx***: start with synthroid 125 µg/d

B. although there are warnings not to do surgery on a hypothyroid patient, the reality is that it takes 3-4 weeks for adequate replacement and hypothyroid patients frequently undergo surgery before then with no untoward effect

3. testosterone replacement: may increase intratumoral levels of estradiol which may promote tumor growth. ∴ wait for stabilization of tumor before starting

PROLACTINOMAS - MANAGEMENT

1. prolactin level **(PRL)** < 500 ng/ml in tumors that are not extensively invasive (*see below* for invasive tumors): PRL may be normalized with surgery
2. PRL > 500 ng/ml: the chances of normalizing PRL surgically are very low[Barrow, 1988 #2669. Algorithm:
   A. if no acute progression (worsening vision…), an initial attempt at purely medical control should be made as the chances of normalizing PRL surgically with pre-op levels > 500 ng/ml are very low[360] (these tumors may shrink dramatically with bromocriptine)
   B. response should be evident by 4-6 weeks
   C. if tumor not controlled medically (≈ 18% will not respond to bromocriptine): surgery followed by reinstitution of medical therapy may normalize PRL

MEDICAL MANAGEMENT

Dopamine agonists

SIDE EFFECTS:[361] (may vary with different preparations) nausea, H/A, fatigue, orthostatic hypotension with dizziness, cold induced peripheral vasodilatation, depression, nightmares and nasal congestion. Side effects are more troublesome during the first few weeks of treatment. Tolerance may be improved by bedtime dosing with food, slow dose escalation, sympathomimetics for nasal congestion, and acetaminophen 1-2 hrs before dosing to reduce H/A. Psychosis and vasospasm are rare side effects that usually necessitates discontinuation of the drug.

bromocriptine (Parlodel®) DRUG INFO

A semi-synthetic ergot alkaloid that binds to dopamine receptors (dopamine agonist) on normal and tumor lactotrophs, inhibiting synthesis and secretion of PRL and other cell processes resulting in decreased cell division and growth. Bromocriptine lowers prolactin level regardless of the whether the source is an adenoma or normal pituitary (e.g. as a result of stalk effect) to < 10% of pretreatment values in most patients. It also frequently reduces the tumor size in 6-8 weeks in 75% of patients with macroadenomas, but only as long as therapy is maintained and only for tumors that actually produce prolactin. Only ≈ 1% of prolactinomas continue to grow while the patient is on bromocriptine. Prolactinomas may enlarge rapidly upon discontinuation of the drug. However, permanent normoprolactinemia can occur (*see below*).

Pregnancy issues: bromocriptine can restore fertility. Continued therapy during pregnancy is associated with a 3.3% incidence of congenital anomalies and 11% spontaneous abortion rate which is the same as for the general population. Estrogen elevation during pregnancy stimulates hyperplasia of lactotrophs and some prolactinomas, but the risk of *symptomatic* enlargement of microadenomas and totally intrasellar macroadenomas is < 3%, vs. 30% risk for macroadenomas[362].

Prolonged treatment with bromocriptine may reduce the chances of surgical cure if this should be chosen at a later date. With a microadenoma, one year of bromocriptine may reduce the surgical cure rate by as much as 50%, possibly due to induced fibrosis[363]. Thus, it is suggested that if surgery is to be done that it be done in the first 6 months of bromocriptine therapy. Shrinkage of large tumors due to bromocriptine may cause CSF rhinorrhea[314].

SIDE EFFECTS: *see above*.

Rx: start with 1.25 mg (half of a 2.5 mg tablet) PO q hs (nighttime dosing reduces some side effects) (vaginal administration is an alternative). Add additional 2.5 mg per day as necessary (based on PRL levels), making a dosage change every 2-4 weeks for microadenomas, or every 3-4 days for macroadenomas causing mass effect. Initial recheck of prolactin level after about 4 weeks at a reasonable dose to verify response. ★ To shrink large tumors or for extremely high PRL levels, higher doses are usually needed initially (e.g. 7.5 mg TID for ≈ 6 mos), and then lower doses may be able to maintain normal levels (typical maintenance dosage: 5-7.5 mg daily (range: 2.5-15 mg) which may be given as a single dose or divided TID). **SUPPLIED**: 2.5 mg scored tabs; 5 mg capsules.

cabergoline (Dostinex®) DRUG INFO

An ergot alkaline derivative that is a selective D_2 dopamine agonist (bromocriptine (*see above*) affects both D_2 and D_1 receptors)[364]. The elimination half-life is 60-100 hrs which usually permits dosing 1-2 times weekly. Control of PRL and resumption of ovulatory cycles may be better than with bromocriptine[365]. **SIDE EFFECTS:** (*see above*) H/A and GI symptoms are reportedly less problematic than with bromocriptine. ✖ Cardiac valve disease[366] affecting the mitral, aortic, and tricuspid valves possibly leading to regurgitation which has not been observed at doses used for prolactinomas (is associated with doses used for Parkinson's disease which are > 10 **x** pituitary doses): recommendation: do not discontinue cabergoline for this reason if dose is < 2 mg/wk. ✖ Contraindications: eclampsia or pre-eclampsia, uncontrolled HTN. Dosage should be reduced with severe hepatic dysfunction.

Rx: Start with 0.25 mg PO twice weekly, and increase each dose by 0.25 mg every 4 weeks as needed to control PRL (up to a maximum of 3 mg per week). Typical dose is 0.5-1 mg twice weekly. Some combine the total dose and give it once weekly. Initial recheck of prolactin level after about 4 weeks to verify response. **SUPPLIED**: 0.5 mg scored tablets.

pergolide (Permax®) DRUG INFO

A long-acting ergot alkaloid dopamine agonist that reduces PRL levels for > 24 hrs. Not FDA approved for hyperprolactinemia. Once daily dosing improves compliance. **SIDE EFFECTS:** *see above*. ✖ Risk of cardiac valve disease (see *cabergoline (Dostinex®)* above).

Rx Start with 0.05 mg PO q hs, and increase by 0.025-0.05 increments (up to a maximum of ≈ 0.25 mg/d) until desired PRL levels are achieved.

Response to medical treatment

Treatment response to DA is assessed with serial prolactin levels as shown in *Table 21-46*. It is uncommon for a prolactinoma to enlarge without an increase in prolactin level[343].

Discontinuation of dopamine agonists: Long-term therapy with DA agonists

has some cytocidal effect on pituitary tissue. In an early report, discontinuation of treatment after 24 months was associated with > 95% recurrence rate[367]. Recent literature suggests a 20-30% chance of normoprolactinemia off medication in select patients[368].

Recommendations[368]: if response to DA agonist is satisfactory, treat for 1-4 years (microadenomas: check prolactin yearly, macroadenomas are more likely to grow and should be checked more often). Microadenomas or macroadenomas that are no longer visible on MRI are candidates for DA agonist withdrawal. For microadenomas: discontinue the drug; for macroadenomas: slowly taper the drug then discontinue. Recurrence rate is highest during 1st year, ∴ check prolactin levels and clinical symptoms every 3 months during the 1st year. Long-term follow up is required, especially for macroadenomas.

Table 21-46 Prolactin level with DA agonist treatment

PRL level (ng/ml)	Recommendation
< 20	maintain
20-50	reassess dose
> 50	consider surgery

ACROMEGALY - MANAGEMENT[323, 325, 369]

Surgery is the primary treatment modality when treatment is indicated.

1. asymptomatic elderly patients do not require treatment since there is little evidence that intervention alters life expectancy in this group
2. if no contraindications, <u>surgery</u> (usually transsphenoidal) is currently the best initial therapy (worse prognosis with macroadenomas) providing more rapid reduction in GH levels and decompression of neural structures (e.g. optic chiasm) and improves the efficacy of subsequent somatostatin analogues[369]. Surgery is not recommended for elderly patients
3. medical therapy (*see page 652*): reserved for:
   A. patients not cured[A] by surgery (reoperation doesn't work very often for acromegaly)
   B. or for those who cannot tolerate surgery (e.g. due to cardiomyopathy, severe hypertension, airway obstruction…, these contraindications may improve with medical therapy and then surgery can be reconsidered)
   C. or for recurrence after surgery or XRT

4. XRT (*see page 656*): for failure of medical therapy. Not recommended as initial treatment. NB: some practitioners use XRT for surgical failure, and employ medical therapy while waiting for XRT to have an effect (GH levels decline very slowly after XRT - *see page 655* for details & for side effects)

Estimated (one-time) cost of transsphenoidal resection: $30,000 in the U.S.

A. the definition of "biochemical cure" with acromegaly is not standardized (*see page 662*), surgery is still helpful for those "not cured" and improves efficacy of other therapies; IGF-1 may take months to normalize after surgery

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MEDICAL THERAPY

1. dopamine agonists **(DAs)**: although not mentioned in the AACE guidelines[321], it may be worth trying a DA to see if the tumor responds (≈ 20% respond). If responsive, DAs are especially well suited for GH tumors that cosecrete PRL
   A. bromocriptine: (*see below*) although it benefits only a minority, a first line drug since it is cheaper than pegvisomant or octreotide and is given PO
   B. cabergoline (*see above*)
   C. pergolide (*see above*)
   D. others: lisuride, depo-bromocriptine (bromocriptine-LAR)
2. somatostatin analogues: indications: as initial medical therapy, or if no response to DAs, some also use this pre-op to improve surgical success rate
   A. octreotide & octreotide-LAR (*see below*)
   B. lanreotide, lanreotide SR & long-acting aqueous gel lanreotide (Autogel)
3. GH antagonists: pegvisomant (*see below*) considered for failures to above (not a primary therapy)
4. combination therapy: may be more effective than individual drugs. Pegvisomant or octreotide + dopamine agonist if no response to 1 drug alone

bromocriptine (Parlodel®) DRUG INFO

Neoplastic somatotrophs may respond fortuitously to dopamine agonists and reduce growth hormone **(GH)** secretion. Bromocriptine lowers GH levels to < 10 ng/ml in 54% of cases, to < 5 ng/ml in only ≈ 12%. Tumor shrinkage occurs in only < 20%. Higher doses are usually required than for prolactinomas. If effective, the drug may be continued but should be periodically withdrawn to assess the GH level. **SIDE EFFECTS:** *see page 651*. Estimated annual cost: $3,200 in the U.S.

Rx For growth hormone tumors that respond to bromocriptine, the usual dosage is 20-60 mg/d in divided doses (higher doses are unwarranted). The maximal daily dose is 100 mg. For dose escalation regimens, *see page 651*.

octreotide (Sandostatin®) DRUG INFO

A somatostatin analogue that is 45 times more potent than somatostatin in suppressing GH secretion but is only twice as potent in suppressing insulin secretion, has a longer half-life (≈ 2 hrs after SQ injection, compared to ≈ minutes for somatostatin), and does not result in rebound GH hypersecretion. GH levels are reduced in 71%, IGF-1 levels are reduced in 93%. 50-66% have normal GH levels, 66% achieve normal IGF-1 levels. Tumor volume reduces significantly in about 30% of patients. Many symptoms including H/A usually improve within the first few weeks of treatment. Annual cost to the patient: at least ≈ $7,800 in the U.S. Usually given in combination with bromocriptine.

After 50 µg SQ injection, GH secretion is suppressed within 1 hr, nadirs at 3 hrs, and remains reduced for 6-8 hrs (occasionally up to 12 hrs). **SIDE EFFECTS:** reduced GI motility and secretion, diarrhea, steatorrhea, flatulence, nausea, abdominal discomfort (all of these usually remit in 10 days), clinically insignificant bradycardia in 15%, cholesterol cholelithiasis (in 10-25%) or bile sludge. Asymptomatic stones require no treatment and routine ultrasonography is not required. Mild hypothyroidism or worsening of glucose intolerance may occur.

Rx: Start with 50-100 µg SQ q 8 hrs. Increase up to a maximum of 1500 µg/d (doses > 750 µg/d are rarely needed). Average dose required is 100-200 µg SQ q 8 hrs.

Sandostatin LAR Depot: long acting release (LAR) form given by *IM* injection. ***Rx***: give a test dose of short acting octreotide SQ in the office, and if

no reaction (e.g. N/V…) begin LAR injections with 20 mg IM q 4 weeks, increase to 30 mg if GH > 5 mU/L just before 4th dose. Control can achieved in some with dosing q 8-12 weeks[370].

pegvisomant (Somavert®) DRUG INFO

A competitive GH-receptor antagonist. Treatment for ≥ 12 mos results in normal IGF-1 levels in 97% of patients[371]. No change in pituitary tumor size has been observed[372]. Indications: failure of somatostatin in patient with GH secreting adenoma (patient is switched to pegvisomant, it is not added to regimen). **SIDE EFFECTS:** significant but reversible liver function abnormalities occur in < 1%. Serum GH increases, probably as a result of loss of negative feedback on IGF-1 production.

Rx: 5-40 mg/d SQ (dose must be titrated to keep IGF-1 in the normal range, to avoid GH deficiency conditions).

CUSHING'S DISEASE - MANAGEMENT

Overall scheme:

1. if pituitary MRI shows a mass: transsphenoidal surgery
2. if pituitary MR is negative (up to 40% of patients with Cushing's disease have negative MRI): perform IPS sampling (*see page 646*)
   A. if IPS sampling is positive: surgery
   B. if IPS sampling is negative: look for source of ACTH (abdominal CT)
3. if biochemical cure (*see page 662* for criteria) is not obtained with surgery:
   A. unlike acromegaly, a partial reduction is not helpful to the patient
   B. consider re-exploration if pituitary source is still suspected
   C. stereotactic radiosurgery or medical therapy (*see below*)
   D. adrenalectomy in appropriate patients (*see below*)

Transsphenoidal surgery

Transsphenoidal surgery is the treatment of choice for most (medical therapy is inadequate as initial therapy since there is no effective pituitary suppressive medication). Cure rates are ≈ 85% for microadenomas (i.e. tumors ≤ 1 cm dia), but are lower for larger tumors. Even with microadenomas,

hemihypophysectomy on the side of the tumor is usually required for cure (the tumor is difficult to completely extirpate) with attendant increased risk of CSF leak. If this fails, consideration should then be for total hypophysectomy. Failure of total hypophysectomy prompts consideration for bilateral adrenalectomy (total hypophysectomy virtually eliminates risk of Nelson's syndrome following adrenalectomy - *see below*).

Stereotactic radiosurgery

Often normalizes serum cortisol levels. Useful for: recurrence after surgery, inaccessible tumors (e.g. cavernous sinus)[373]…

Adrenalectomy

Total bilateral adrenalectomy **(TBA)** corrects hypercortisolism in 96-100%[316] (unless there is an extra-adrenal remnant), but lifelong gluco- and mineralo-corticoid replacement are required and up to 30% develop Nelson's syndrome (*see page 639*) (incidence reduced by total hypophysectomy or possibly by pituitary XRT). Indications: continued hypercortisolism with:

1. non-resectable pituitary adenoma
2. failure of medical therapy to control symptoms after transsphenoidal surgery
3. life-threatening Cushing's disease **(CD)**
4. CD with no evidence of pituitary tumor (testing should include high-dose DMZ suppression test (*see page 646*) and/or inferior petrosal sinus sampling (*see page 646*))

Follow-up after TBA to rule-out Nelson's syndrome: there is no standardized regimen. Suggestion: check serum ACTH levels q 3-6 months **x** 1 year, q 6 months **x** 2 years, q year thereafter. A pituitary MRI is done if an ACTH level is > 100 ng/L, otherwise, annual MRIs are sufficient[318] **x** 3 years and then if ACTH levels remain low, get an MRI every other year.

Medical therapy

For patients who fail surgical therapy or for whom surgery cannot be tolerated, medical therapy and/or radiation are utilized. Occasionally may be used for several weeks prior to planned surgery to control significant manifestations of hypercortisolism (e.g. diabetes, HTN, psychiatric disturbances…, *see page 638*).

Ketoconazole (Nizoral®)[361]: an antifungal agent that blocks adrenal steroid synthesis. The initial drug of choice. Over 75% of patients have normalization of urinary free cortisol and 17-hydroxycorticosteroid levels. **Side effects:** reversible elevations of serum hepatic transaminase (in 15%), GI discomfort, edema, skin rash. Significant hepatotoxicity occurs in 1 of 15,000 patients. Watch for evidence of adrenal insufficiency (*see page 32*).

Rx Start with 200 mg PO BID. Adjust dosage based on 24-hr urine free cortisol and 17-hydroxycorticosteroid levels. Usual maintenance doses 400-1200 mg daily in divided doses (maximum of 1600 mg daily).

Aminoglutethimide (Cytadren®)[361]: inhibits the initial enzyme in the synthesis of steroids from cholesterol. Normalizes urinary free cortisol in ≈ 50% of cases. **Side effects:** dose-dependent reversible effects include sedation, anorexia, nausea, rash and hypothyroidism (due to interference with thyroid hormone synthesis).

Rx Start with 125-250 mg PO BID. Effectiveness may diminish after several months and dose escalation may be needed. Generally do not exceed 1000 mg/d.

Metyrapone (Metopirone®): inhibits 11-ß-hydroxylase (involved in one of the final steps of cortisol synthesis) may be used alone or in combination with other drugs. Normalizes mean daily plasma cortisol in ≈ 75%. **Side effects:** lethargy, dizziness, ataxia, N/V, primary adrenal insufficiency, hirsutism and acne.

Rx Usual dose range is 750-6000 mg/d usually divided TID with meals. Initial effectiveness may diminish with time.

Mitotane (Lysodren®): related to the insecticide DDT. Inhibits several steps in glucocorticoid synthesis, and is cytotoxic to adrenocortical cells (adrenolytic agent). 75% of patients enter remission after 6-12 months of treatment, and the medication may sometimes be discontinued (however hypercortisolism may recur). **Side effects:** may be limiting, and include anorexia, lethargy, dizziness, impaired cognition, GI distress, hypercholesterolemia, adrenal insufficiency (which may necessitate supernormal doses of glucocorticoids for replacement due to induced glucocorticoid degradation).

Rx Start with 250-500 mg PO q hs, and escalate dose slowly. Usual dose range is 4-12 gm/d usually divided TID-QID. Initial effectiveness may diminish with time.

Cyproheptadine (Periactin®): a serotonin receptor antagonist that corrects the abnormalities of Cushing’s disease in a small minority of patients, suggesting

that some cases of "pituitary" Cushing's disease are really due to a hypothalamic disorder. Combined therapy with bromocriptine may be more effective in some patients. **Side effects:** sedation & hyperphagia with weight gain usually limit usefulness.

Rx Usual dosage range: 8-36 mg/d divided TID.

Thyrotropin (TSH)-secreting adenomas - management

1. transsphenoidal surgery has been the traditional first-line treatment[327]. These tumors may be fibrous and difficult to remove[374]
2. for incomplete resection: post-op XRT is employed
3. if hyperthyroidism persists: medical therapy is added with agents including octreotide, bromocriptine (more effective for tumors that cosecrete PRL), and oral cholecystographic agents (which inhibit conversion of T_4 to T_3) e.g. iopanoic acid

Medical therapy

Normal and neoplastic anterior hypophyseal thyrotroph cells possess somatostatin receptors and most respond to octreotide (*see below*). Occasionally, beta-blockers or low-dose antithyroid drugs (e.g. Tapazole® (methimazole) ≈ 5 mg PO TID for adults) may additionally be required.

Octreotide (Sandostatin®)

Doses required are usually < than with acromegaly. TSH levels decline by > 50% in 88% of patients, and become normal in ≈ 75%. T_4 and T_3 levels decrease in almost all, with 75% becoming normal. Tumor shrinkage occurs in ≈ 33%.

Rx Start with 50-100 μg SQ q 8 hrs. Titrate to TSH, T_4 and T_3 levels.

Radiation therapy for pituitary adenomas

Conventional EBXRT usually consists of 40-50 Gy administered over 4-6 weeks.

Side effects: Radiation injury to the remaining normal pituitary results in hypocortisolism, hypogonadism, or hypothyroidism in 40-50% of patients after 10 years. It may also injure the optic nerve and chiasm (possibly causing blindness), cause lethargy, memory disturbances, cranial nerve palsies, and tumor necrosis with hemorrhage and apoplexy. Cure rates but also complications are higher after proton beam therapy.

Recommendation: Radiation therapy should not be routinely used following surgical removal. Follow patient with yearly MRI. Treat recurrence with repeat operation. Consider radiation if recurrence cannot be removed and tumor continues to grow.

Nonfunctional tumors

In one series of 89 nonfunctioning pituitary tumors ranging 0.5-5 cm diameter (mean = 2 cm) not totally resected because of involvement of cavernous sinus (or other inaccessible sites), half were treated with radiation therapy **(XRT)**. The recurrence rate was neither lower (and was actually higher) nor later in the XRT group[293]. However, another series of 108 pituitary macroadenomas found the recurrence rates shown in *Table 21-47* which tend to favor radiation therapy.

When used, doses of 40 or 45 Gy in 20 or 25 fractions, respectively, is recommended[376]. The oncocytic variant of null cell pituitary tumors appears to be more radioresistant than the nononcocytic undifferentiated cell adenoma[376].

Acromegaly

Not the preferred initial treatment. Works better with lower initial GH levels. In most patients, GH levels begin to fall during the first year after XRT, dropping by ≈ 50% after 2 years, and decrease gradually thereafter, reaching ≤ 10 ng/ml in 70% of patients after 10 years. It takes up to 20 years for 90% of patients to achieve GH levels < 5 ng/ml. During this latency period, patients are exposed to unacceptably high levels of GH (octreotide may be used while waiting). Patients are also still at risk for radiation side effects mentioned above. Options include: EBRT, stereotactic radiosurgery (about equally effective). Estimated cost: $20,000.

Cushing's disease

XRT corrects hypercortisolism in 20-40%, and produces some improvement in another 40%. Improvement may not be seen for 1-2 yrs post treatment.

Table 21-47 Recurrence rate of pituitary tumors removed transsphenoidally*

Extent of removal	Post-op XRT?	Recurrence rate
subtotal	no	50%
gross total		21%

subtotal	yes	10%
gross total		0

* 108 macroadenomas, 6 mos to 14 years follow-up[375]

SURGICAL TREATMENT FOR PITUITARY ADENOMAS

MEDICAL PREPARATION FOR SURGERY

1. stress dose steroids: given to all patients during and immediately after surgery
2. hypothyroidism: ideally, hypothyroid patients should have > 4 weeks of replacement to reverse hypothyroidism, however:
   - ✖ do not replace thyroid hormone until the adrenal axis is assessed; giving thyroid replacement to a patient with hypoadrenalism can precipitate adrenal crisis. If hypoadrenal, begin cortisol replacement first, may begin thyroid hormone replacement after 24 hours of cortisol
   - surgery is done frequently on patients with hypothyroidism and appears to be tolerated well in the vast majority of cases

SURGICAL APPROACHES

1. transsphenoidal: an extra-arachnoid approach, requires no brain retraction, no external scar (aside from where a fat graft is procured, if used). Usually the procedure of choice. Indicated for microadenomas, macroadenomas without significant extension laterally beyond the confines of the sella turcica, patients with CSF rhinorrhea, and tumors with extension into sphenoid air sinus
   A. sublabial
   B. trans-nares: an alotomy may be used to enlarge the exposure through the nares if necessary
2. transethmoidal approach[377] (p 343-50)
3. transcranial approaches:
   A. indications: most pituitary tumors are operated by the transsphenoidal technique (*see above*), even if there is significant suprasellar extension. However, a craniotomy may be indicated for the following[329]:
      1. minimal enlargement of the sella with a large suprasellar mass,

especially if the diaphragma sellae is tightly constricting the tumor (producing a "cottage loaf" tumor) and the suprasellar component is causing chiasmal compression[378 (p 124)]
2. extrasellar extension into the middle fossa that is larger than the intrasellar component
3. unrelated pathology may complicate a transsphenoidal approach: rare, e.g. a parasellar aneurysm
4. unusually fibrous tumor that could not be completely removed on a previous transsphenoidal approach
5. recurrent tumor following a previous transsphenoidal resection

B. choices of approach
1. subfrontal: provides access to both optic nerves. May be more difficult in patients with prefixed chiasm
2. frontotemporal (pterional): places optic nerve and sometimes carotid artery in line of vision of tumor. There is also incomplete access to intrasellar contents. Good access for tumors with significant lateral extrasellar extension
3. ✖ subtemporal: usually not a viable choice. Poor visualization of optic nerve/chiasm and carotid. Does not allow total removal of intrasellar component

TRANSSPHENOIDAL SURGERY

Booking the case - transsphenoidal surgery

Also see defaults & disclaimers (*page v*) and pre-op orders (*page 660*).

1. position: supine, horseshoe head rest or (especially if image guided navigation is used) pin headholder
2. equipment:
   A. microscope
   B. C-arm (if used)
   C. image guided navigation system (if used)
   D. endoscopy cart for cases performed endoscopically (surgeon preference)
3. instrumentation: transsphenoidal instrument set (usually includes speculum, curettes, long instruments including bipolars)

4. some surgeons use ENT to perform the approach and closure and for follow-up
5. post op: ICU
6. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: removal of pituitary tumor through the nose, possible placement of fat graft from abdomen
   B. alternatives: surgery through the skull (trans-cranial), radiation
   C. complications: CSF leak with possible meningitis, problems with pituitary hormones which may sometimes be permanent (which would require life-time replacement therapy), injury to optic nerve with visual loss, injury to carotid artery with possible bleeding and/or stroke

Technique

For pre- and post-op orders, *see below*.

Details of the surgery are beyond the scope of this text, see references[378-381]. A brief summary of the procedure:

1. lumbar drain: may be used with some macroadenomas to inject fluid in order to help bring the tumor down (*see below*), also may be used for post-op CSF drainage following transsphenoidal repair of CSF fistula
2. medications (in addition to pre-op meds, *see below*): intraoperatively 100 mg hydrocortisone IV q 8 hrs
3. positioning
   A. elevate thorax 10-15°: reduces venous pressure
   B. position option 1: surgeon standing to right of patient
      1. shoulder-roll
      2. top of head canted slightly to left
      3. <u>extend</u> neck slightly with the head in either a Mayfield head-holder (mandatory if image-guided navigation is to be used) placed low or in AP orientation (to prevent obscuring the sella turcica on lateral fluoroscopy) or on a horse-shoe headrest
      4. ET tube positioned down and to patient's <u>left</u> (to get it out of the way)
      5. microscope: observer's eyepiece on the <u>left</u>
   C. position option 2: surgeon standing above patient's head
      1. head pointing straight up towards ceiling, neck slightly extended
   D. abdomen or right thigh is prepped for fat graft
4. C-arm fluoro: image-guided navigation can eliminate the need for fluoro.

Orient the C-arm for a true lateral by aligning the mandibular rami and/or by superim-posing the floor of the left and right frontal fossae. If this proves difficult, lay a Penfield 4 on the inion oriented from lateral canthus to lateral canthus, then aim the fluoro to shoot "down the barrel" of the Penfield 4

5. after approach to floor of sella is complete (*see below*), outline the upper and lower boundaries of the sella using an instrument (e.g. suction tip) under fluoro (obtain hard-copy of images for documentation purposes)
6. opening the sellar floor:
   A. starting the opening: open exactly in the midline using the nasal septum as a landmark (NB: the septum of the sphenoid sinus is unreliable as a midline indicator, and often curves inferiorly towards one of the carotid arteries).
      1. macroadenomas may have thinned the bone to the point that it just flakes off
      2. otherwise, use a bayoneted chisel or high-speed diamond burr to start the opening
   B. use a Kerrison rongeur to expand the opening. ✖ CAUTION: stay away from the extreme lateral sella to avoid entering the cavernous sinus or injuring the carotid artery
7. coagulate the dura centrally in an "X" pattern (NOT "+" pattern) with bipolar cautery. Macroadenomas may cause yellowish discoloration of the dura directly over the tumor
8. consider aspirating through dura with a 20 gauge spinal needle to R/O large venous sinus (dura often has bluish discoloration), aneurysm, or empty sella
9. incise the dura in the "X" pattern the midline with a #11 scalpel on a bayonetted handle
10. tumor removal
    A. **macroadenoma**:
       1. gently bring tumor into the field with ring curettes, and remove with pituitary rongeurs or aspirate with suction. Some tumors are very fibrous and may be difficult to remove
       2. do not pull on the lateral component of the tumor with pituitary rongeur due to risk of injuring carotid artery
       3. if the suprasellar component will not come down, it may be brought down by having the anesthesiologist inject 5 ml aliquots of saline into a lumbar drain while monitoring blood pressure and

pulse[378 (p 135), 382]

4. once the tumor is debulked internally, try to develop a plane between the tumor capsule and the pituitary. A good place to start looking is inferiorly where the dura can be separated from the tumor capsule and then followed on the surface. Sometimes the tumor capsule cannot be removed due to severe bleeding
5. complete tumor removal is often not possible, and the goal of the surgery then is "containment"
6. endoscopic techniques and image guided navigation may be employed to assist in removal of macroadenomas

B. **microadenoma**:
   1. if the side of the tumor is known, begin exploration of the gland on that side by making incision with #11 blade and using a dissector to try and locate the tumor (like a "grain of rice in a blueberry")
   2. for Cushing's disease, if no tumor is identified on pre-op MRI[317]:
      a. intraoperative ultrasound may help localize tumor in ≈ 70% of cases[357] but a specialized U/S probe is required
      b. if IPS sampling showed a lateralizing ACTH gradient
         i. start with a paramedian incision on the side of the higher ACTH gradient
         ii. if no adenoma is encountered, the contralateral paramedian and then midline incisions are used to explore the gland
      c. if IPS sampling and MRI do not suggest tumor location: the gland is explored sequentially with 2 paramedian incisions and then a midline incision
      d. if the adenoma cannot be found, a hemihypophysectomy is performed on the side of higher ACTH levels if IPS sampling shows a lateralizing gradient, or on the side with more suspicious tissue on frozen section. Total hypophysectomy is not routinely performed[317]

C. most adenomas are purplishgrey and easily aspirated, however some may be more fibrous. The normal pituitary gland is firm and rubbery (the adenohypophysis is orange-pink, the neurohypophysis is a whitishgrey), and normally does not curette very easily

D. use image guidance or fluoro to determine approximate location of diaphragma sellae. Do not go cephalad to this to avoid a CSF leak, to avoid entering the circular venous sinus in the dura here and to avoid trauma to the optic chiasm

11. after removal of macroadenoma, check depth of tumor bed on fluoro or image guidance, and make sure it correlates with approximate tumor volume on MRI
12. the sella may be packed in a number of ways[381], one method:
    A. place muscle or fat in defect within sella: some recommend against the use of muscle because it always putrifies[378 (p 129)]. Do not overpack to avoid recreating mass effect with the graft
    B. recreate the floor of the sella using nasal cartilage placed within the sella. Alternatively, a nonporous Medpor® polyethylene transsphenoidal sellar implant (Porex Surgical Products http://www.porexsurgical.com) may be used
    C. pack sphenoid sinus with fat from abdomen (option: fat with fascia on surface)
    D. fibrin glue may optionally be used to help hold any of these components in place

Approach to sphenoid sinus: often done by ENT. One method:
1. insert temporary speculum into nose. For this discussion, the right nares will be described
2. use endoscope to locate middle concha. Follow this posteriorly to identify os into sphenoid sinus
3. inject local anesthetic with epinephrine to blanch mucosa
4. insert sickle knife into os with sharp side facing the septum (medially) and incise the mucosa as the knife is drawn outward
5. use a Freer to dissect the thusly created mucosal flaps off the medial septum (pull one up, the other down)
6. break through the posterior part of the septum so that both sides of the floor of the sphenoid sinus are exposed. Cartilage or bone from this step is saved to use later in reconstructing the floor of the sella if desired
7. open the floor of the sphenoid and take it all the way to the right os (you will probably not see the left os)
8. place the Hardy speculum or equivalent
9. strip mucosa off the walls of the sphenoid sinus using a Blakely and slow pulling motion

Intraoperative disasters: usually related to loss of landmarks[378].
1. entry into carotid artery: heralded by profuse arterial bleeding that can usually be packed off (using fat/fascia graft from thigh or abdomen may

help). The operation is halted, and a post-op arteriogram must be done. If a pseudoaneurysm is identified angiographically, it must be eliminated before a potentially lethal rupture; accomplished either by endovascular techniques or by surgical trapping with clips above and below

2. opening through the clivus and erroneous biopsy of the pons
3. opening through the floor of the frontal fossa with entry into inferior frontal lobes

Peri-operative complications

1. hormonal imbalance:
   A. acute post-op concerns:
      1. alterations in ADH: transient abnormalities are common (*see page 661* for typical post-op patterns) including DI. DI lasting > 3 mos is uncommon
      2. cortisol deficiency → hypocortisolism → Addisonian crisis if severe
   B. long-term: hypopituitarism in ≈ 5% (retrospective series[383])
      1. TSH deficiency → hypothyroidism → (rarely) myxedema coma if severe
      2. adrenal insufficiency
      3. deficiency of sex hormones → hypogonadotrophic hypogonadism
2. secondary empty sella syndrome (chiasm retracts into evacuated sella → visual impairment)
3. hydrocephalus with coma[384]: may follow removal of tumors with suprasellar extension (transsphenoidally or transcranially). Consider ventriculostomy placement if hydrocephalus is present (even if not symptomatic). Possible etiologies:
   A. traction on the attached 3rd ventricle
   B. cerebral edema due to vasopressin release from manipulation of the pituitary and/or stalk
   C. tumor edema following resection
4. infection
   A. pituitary abscess[385, 386]
   B. meningitis
5. CSF rhinorrhea (fistula): 3.5% incidence[375]
6. carotid artery rupture: rare. May occur intraoperatively (*see above*) or in

delayed fashion after surgery, often ≈ day 10 post-op (due to breakdown of fibrin around carotid, or possibly due to rupture of a pseudoaneurysm created at surgery)
7. entry into cavernous sinus with possible injury of any structure within
8. nasal septal perforation

FRONTOTEMPORAL (PTERIONAL) APPROACH

A right sided approach is usually employed (less risk to dominant hemisphere). Exceptions: when the left eye is the side of worse vision; if there is predominant left sided tumor extension; if there is other pathology on the left (e.g. aneurysm).

Positioning is that same as for ACoA aneurysm with the head turned 60° to the side (*see page 159*). The frontal lobe is elevated, and the temporal tip is gently retracted posteriorly. Bridging veins to the temporal tip must be coagulated to avoid rupture, as for any pterional approach. The approach is similar to that for an ACoA aneurysm (i.e. more emphasis is placed on frontal lobe elevation than on temporal tip retraction), except that unlike ACoA aneurysm, exposure of the ICA is not needed because proximal control is not necessary.

The tumor capsule can usually be seen between the two optic nerves. The capsule is coagulated with bipolar cautery, and is incised. The tumor is then debulked from within. By staying within the capsule, risk of injury to the pituitary stalk and optic chiasm is minimized. Significant amounts of tumor can be removed by aspiration if it is soft and suckable.

✖ Caution: the blood supply to the optic chiasm is from the inferior aspect. Skeletonizing the chiasm or attempting to tease away tumor adherent to it may worsen vision.

PERI-OPERATIVE MANAGEMENT

Pre-op orders

1. Polysporin® ointment (PSO) applied in both nostrils the night before surgery
2. antibiotics, one of the following regimens may be used:
   • chloramphenicol 500 mg IVPB at 11 PM & 6 AM
   OR
   • chloramphenicol 500 mg PO at MN & IV at 6 AM; ampicillin 1 gm PO

at MN & IV at 6 AM

OR

- Unasyn® 1.5 gm (1 gm ampicillin + 0.5 gm sulbactam) IVPB at MN & 6 AM

3. steroids, either:
   - hydrocortisone sodium succinate (Solu-Cortef®) 50 mg IM at 11 PM & 6 AM. On call to OR: hang 1 L D_5 LR + 20 mEq KCl/l + 50 mg Solu-Cortef at 75 ml/hr

   OR

   - hydrocortisone 100 mg PO at MN & IV at 6 AM
4. intra-op: continue 100 mg hydrocortisone IV q 8 hrs

Post-op orders

1. intake & output (I's & O's) q 1 hr; urine specific gravity **(SG)** q 4° and anytime urine output **(UO)** > 250 ml/hr
2. activity: BR with HOB @ 30°.
3. diet: ice chips PRN. Patient is not to drink through a straw[A]
4. no incentive spirometry[A]
5. <u>IVF</u>: base IV D5 1/2 NS + 20 mEq KCl/L at appropriate rate (75-100 ml/hr) PLUS: replace UO > base IV rate ml for ml with 1/2 NS.

   NB: if patient receives significant fluids intraoperatively, then they may have an appropriate post-op diuresis, in which case consider replacing only ≈ 2/3 of UO > base IV rate with 1/2 NS
6. meds
   A. antibiotics: continue chloramphenicol 500 mg IVPB q 6 hr (also continue ampicillin if used pre-op), change to PO when tolerated, D/C when nasal packing removed

   B. steroids (post-op steroids are required until the adequacy of endogenous steroids is established, especially with Cushing's disease, *see below*). Either:
      - hydrocortisone 50 mg IM/IV q 6 hrs, on POD #2 change to prednisone 5 mg PO q 6 hrs x 1 day, then 5 mg PO BID, D/C on POD #6

      OR

      - hydrocortisone 50 mg IM/IV/PO BID, taper 10 mg/dose/day to physiologic dose of 20 mg q AM and 10 mg q PM until adrenal axis assessed

C. <u>diabetes insipidus</u> **(DI)**: *see below* for typical patterns. Criteria: U.O. > 250 ml/hr **x** 1-2 hrs, <u>and</u> SG < 1.005 (usually < 1.003). If DI develops, attempt to keep up with fluid loss with IVF (*see above*); if rate is too high for IV or PO replacement (> 300 cc/hr **x** 4 hrs or > 500 cc/hr **x** 2 hrs), check urine S.G. and if < 1.005 then give a vasopressin preparation (*see below*, or see *Table 2-7*, page 17). *Caution*: danger of overtreating in case of triphasic response (*see below*), therefore use EITHER:

- 5 U aqueous vasopressin (Pitressin®) IVP/IM/SQ q 6 hrs PRN

OR

- desmopressin (DDAVP®) injection SQ/IV titrated to UO. Usual adult dose: 0.5-1 ml (2-4 μg) daily in 2 divided doses

AVOID

✖ avoid tannate oil suspension, because of erratic absorption and it is a long acting preparation

THEN: when nasal packs out, either

- intranasal DDAVP (100 μg/ml): range 0.1-0.4 ml (10-40 μg) intranasally BID (typically 0.2 ml BID) PRN

OR

- clofibrate (Atromid S®) 500 mg PO QID (does not always work)

7. labs: renal profile with osmolarity q 6 hrs, 8 A.M. serum cortisol
8. nasal packs: remove on post-op day 3-6

A. to avoid negative pressure on sphenoid sinus with risk of aggravating CSF fistula

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Urinary output: patterns of postoperative <u>diabetes insipidus</u>

Manage diabetes insipidus **(DI)** as described above. Post-op DI generally follows one of three patterns[387] (see *Diabetes insipidus*, page 15 for details):

1. transient DI: lasts until ≈ 12-36 hrs post-op
2. "prolonged" DI: lasts months, or may be permanent
3. "**triphasic response**" (least common). Summary: ① DI → ② normalization or SIADH-like picture → ③ DI (again)

Assessment for postoperative ACTH (corticotropin)

reserve

If patient was not hypocortisolemic pre-op:

1. taper and stop hydrocortisone 24-48 hrs post-op. Then, check 6 AM serum cortisol level 24 hrs after discontinuing hydrocortisone and interpret the results as shown in *Table 21-48* 352. If there is any question about reserve, the patient can be discharged on hydrocortisone 50 mg PO q AM and 25 mg PO q PM until adrenal reserve can be formally assessed
2. alternatively, if the patient goes home on hydrocortisone and was not on it pre-op, taper it over 2-3 weeks to 20 mg po q AM and 10 mg q 4 PM (a little above maintenance to provide for some stress coverage) for several days, then hold the PM dose and check an 8 AM serum cortisol then next day and as soon as the blood is drawn have the patient take their morning dose and resume regular dosing until the test results are available. If this 8 AM cortisol shows any significant function, then taper the patient off hydrocortisone
3. **metyrapone** (Metopirone®) test: useful if there is suspicion of reduced reserve of pituitary ACTH production. All patients should have a cosyntropin stimulation test first to rule-out primary adrenal insufficiency (*see page 647*). ✖ Do not do this test if there is primary adrenal insufficiency. ✖ Do not do this test as an outpatient. Metyrapone inhibits 11-ß-hydroxylation in the adrenal cortex, reducing production of cortisol and corticosterone with concomitant increase of serum 11-deoxycortisol precursors and its 17-OHCS metabolites which appear in the urine. In response, a normal pituitary increases ACTH production. **Test**: give 2-3 grams metyrapone PO at midnight; a normal response is a serum 11-deoxycortisol level > 7 µg/dl the next morning. CAUTION: in patients with very little reserve, the reduced cortisol may provoke adrenal insufficiency (this test is safer than the higher doses used for urinary 17-OHCS testing)

Table 21-48 Interpretation of 6 AM cortisol levels

6 AM cortisol	Interpretation	Management
≥ 9 µg/dl	normal	no further tests or treatment
3-9 µg/dl	possible ACTH deficiency	place patient on hydrocortisone* (*see page 31*)
≤ 3 µg/dl	ACTH deficient	

* perform cosyntropin stimulation test (see page 647) 1 month post-op; D/C steroids if normal; if subnormal, then permanent replacement required

Postoperative CT/MRI scan

A study using CT in 12 patients with macroadenomas following transsphenoidal surgery without radiation therapy demonstrated that the maximal height of the pituitary "mass" did not return to normal immediately post-op (even with total tumor removal), rather a period of 3-4 months was required[388].

> Σ The optimal timing of the initial post-op CT or MRI to function as a baseline to ruleout future recurrence after transsphenoidal surgery is ≈ 3-4 months post-op.

OUTCOME

FOLLOWING TRANSSPHENOIDAL SURGERY

In cases with compression of the optic apparatus, there can be significant improvements in vision following surgery[375, 389].

General information:

1. endocrinologic cure was attained in 25% of prolactin-secreting tumors, and in 20% of growth hormone-secreting tumors[A] (*see below*)
2. gross total removal was unusual in tumors with > 2 cm suprasellar extension[A]
3. recurrence incidence: ≈ 12%, with most recurring 4-8 years post-op[A]
4. Cushing's disease: surgical cure rates are ≈ 85% for microadenomas (i.e. tumors ≤ 1 cm dia), but are lower for larger tumors (*see below*)

BIOCHEMICAL OUTCOME

Acromegaly Criteria of biochemical cure: The criteria for biochemical cure of acromegaly is not standardized. There may be a discord between IGF-1 levels and mean GH levels[370]. Many use a GH cutoff level; range of levels described: < 2.5-5 ng/ml. Others feel that an elevated IGF-1 represents lack of cure even if GH < 5. However, normal IGF-1 levels may not be mandatory[390]. Still others require a normal IGF-1 AND a normal response to an oral glucose suppression test **(OGST)** (*see page 648*).

Low GH levels that do not also suppress to < 1 ng/ml after an OGST are considered *controlled* but not cured (even with normal IGF-1 levels)[321]. If asymptomatic, expectant management with close follow-up is recommended[321].

> Biochemical cure criteria for acromegaly is not standardized. Recommendation[321]:

Σ 1) IGF-1 levels within age-matched reference range
2) basal (morning) serum GH level < 5 ng/ml, AND GH nadir < 1 ng/ml in OGST

Outcome: Transsphenoidal surgery results in biochemical cure in 85% of cases with adenomas < 10 mm diameter, no evidence of local invasion, and random GH levels < 40 ng/ml pre-op. Overall, ≈ 50% of all acromegalics undergoing transsphenoidal surgery had a biochemical cure[391]. Only 30% of macroadenomas and very few with marked suprasellar extension have surgical cure. Patients not cured with surgery require lifelong medical suppression. These tumors may also recur years later after apparent cure. Patients should be monitored every 6-12 months for recurrence[321].

Cushing's disease

There are numerous methodologies for determining biochemical cure for Cushing's disease. One difficulty is that exogenous steroids are often given post-op to avoid potential hypoadrenalism or Addisonian crisis or for nausea. Some options:

1. immediate post-op early morning cortisol levels[317]:
   A. all steroids are withheld post-op (including dexamethasone as an antiemetic) unless biochemical and/or clinical[B] evidence of hypocortisolism. ✖ Requires close monitoring and administration of steroids if symptoms develop
   B. serum ACTH and cortisol levels are drawn between 6-9:00 AM on post-op days 1 & 2
   C. early remission defined as a <u>lowest</u> cortisol level ≤ 140 nmol/L (≤ 5 μg/dl)
      1. 97% (31/32) patients with early remission had sustained remission with mean follow-up of 32 months
      2. only 12.5% (1/8) without early remission showed evidence of sustained remission
      3. this has been used to select patients for possible early re-exploration
      4. early ACTH levels usually drop, but do not consistently become sub-normal and are not reliable in predicting sustained remission[317]
2. provocative tests
   A. overnight low-dose dexamethasone suppression test: an AM cortisol

level on post-op day 3 that is ≤ 8 µg/dl after an overnight 1 mg dexamethasone suppression test is predictive of sustained remission in 97%[392]

B. CRH stimulation test[393]

3. measurements usually conducted 3 days to 2 weeks post-op following 24 hours of steroid cessation after initial post-op coverage with glucocorticoids
   A. 24-hour urinary free cortisol
   B. serum cortisol: the criteria of a cortisol level < 50 nmol/l (< 1.8 µg/dl)[394-396] is probably too stringent[317, 397, 398]
   C. serum ACTH

A. based on a series of 108 macroadenomas[375]

B. clinical signs of hypocortisolism: nausea, anorexia, H/A, arthralgias

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The overall remission rate since 1980 is 64-93%, with the highest rates (86-98%) in patients with noninvasive microadenomas identifiable on MRI[317].

Following effective treatment, all of the following usually improve but may not normalize:

1. HTN and hyperglycemia: within ≈ 1 year
2. osteoporosis related to CD: over ≈ 2 years
3. psychiatric symptoms

Thyrotropin (TSH)-secreting adenomas

Following debulking, small amounts of residual tumor may continue to produce sufficient TSH for hyperthyroidism to persist[374]. Following surgery + XRT, only ≈ 40% achieve a cure (defined as no residual tumor at surgery or on imaging, and normal free T_3 with TSH levels at or below normal).

MANAGEMENT OF RECURRENT PITUITARY ADENOMAS

For tumors demonstrating significant regrowth or symptoms following initial resection, consideration for re-resection may be given. Once the tumor is debulked, consideration should be given to XRT, either immediately following the second operation, or, if recurrence after a second operation then almost

certainly after a third debulking.

21.2.10. Craniopharyngioma

Craniopharyngiomas **(CP)** are tumors that develop from residual cells of Rathke’s pouch (*see page 109*), and tend to arise from the anterior superior margin of the pituitary. They are lined with stratified squamous epithelium. Some CP may arise primarily within the third ventricle[399]. Almost all CP have solid and cystic components; fluid in the cysts varies, but usually contains cholesterol crystals. CP do not undergo malignant degeneration; but difficulty in cure makes them malignant in behavior[267 (p 905-15)]. CP are distinct from Rathke’s cleft cyst, but share some similarities (*see below*).

Calcification: microscopically 50%. Plain x-ray: 85% in childhood, 40% in adults.

EPIDEMIOLOGY

Incidence: 2.5-4% of all brain tumors; about 50% occur in childhood (9% of Matson’s series). Peak incidence: age 5-10 yrs.

ANATOMY

Arterial supply: usually small feeders from ACA and A-comm, or from ICA and Pcomm (do not receive blood from PCA or BA-bifurcation unless blood supply of floor of third ventricle is parasitized).

SURGICAL TREATMENT

Pre-op endocrinologic evaluation

As for pituitary tumor (*see page 643*). Hypoadrenalism may be corrected rapidly, but hypothyroidism takes longer; either condition can increase surgical mortality.

Approach

Usually via large right frontotemporal flap as low as possible along base of frontal fossa (lateral sphenoid wing rongeured/drilled). Approach to tumor is extra-axial, whether subfrontal or frontotemporal. All tumors should be aspirated (even if they appear solid radiographically). Then, with microscope, possible

approaches include:

1. subchiasmatic: through space between optic nerves and anterior to chiasm. It was thought that a "**prefixed chiasm**" (i.e. congenitally short optic nerves with chiasm unusually close to the planum sphenoidale) was more common in patients with CP, making this approach more difficult. However, in reality the chiasm is probably bowed anteriorly by the tumor within the third ventricle giving the illusion of a prefixed chiasm in most cases
2. opticocarotid (between right ICA and right optic nerve/tract)
3. lamina terminalis (tumor often needs to be brought down and removed subchiasmatically)[399, 400]
4. lateral to carotid artery
5. transfrontal-transsphenoidal: drill off tuberculum sellae

Alternative approaches to frontotemporal

1. pure transsphenoidal: if dark fluid is aspirated with no CSF evident, it is possible to leave a stent from the tumor cavity to the sphenoid air-sinus to permit continued drainage
2. transcallosal: strictly for tumors limited to the third ventricle
3. a combined subfrontal/pterional approach capitalizes on the advantages of each (head is positioned with slight lateral rotation)

Spare the following structures: small arterial feeders to undersurface of the chiasm (major supply) and tract; at least a remnant of pituitary stalk (recognized by unique pattern of longitudinal striations which are the long portal veins). If the tumor easily pulls down from above then this is permissible, however do not pull too hard or else hypothalamic injury may result.

Post-op

1. steroids: these patients are all considered hypoadrenal. Give hydrocortisone in physiologic doses (for mineralocorticoid activity) in addition to dexamethasone (glucocorticoid that treats edema) taper (*see page 31*). Taper steroids slowly to avoid aseptic (chemical) meningitis
2. **diabetes insipidus (DI)**: often shows up early. May be part of a "triphasic response" (see *Urinary output: patterns of postoperative diabetes insipidus*, page 661). Best managed initially with fluid replacement. If necessary, use short acting vasopressin (prevents iatrogenic renal shutdown if a SIADH-like phase develops during vasopressin therapy)

Outcome

5-10% mortality in most series, most from hypothalamic injury (unilateral hypothalamic lesions are rarely clinically evident; bilateral injuries may produce hyperthermia and somnolence; damage to anterior osmoreceptors may → loss of thirst sensation). Five year survival is ≈ 55-85% (range from 30-93% has been reported).

Radiation

Controversial. **Side effects:** include endocrine dysfunction, optic neuritis, dementia. Post-op XRT probably helps prevent regrowth when residual tumor is left behind[401], however, in pediatric cases it may be best to postpone XRT (to minimize deleterious effect on IQ, *see page 771*), recognizing that reoperation may be necessary for recurrence.

Recurrence

Most recurrences are in < 1 year, few > 3 yrs (very delayed recurrence usually follow what was thought to be "total" removal). Morbidity/mortality is higher with re-operation.

21.2.11. Rathke's cleft cyst

Rathke's cleft cyst **(RCC)** are nonneoplastic lesions that are thought to be remnants of Rathke's pouch. They are primarily intrasellar, and are found incidentally in 13-23% of necropsies[402]. The adenohypophysis arises from proliferation of the anterior wall of Rathke's pouch, and so RCC have a similar lineage to pituitary adenomas and are rarely found together[403]. RCC are often discussed in contrast to craniopharyngiomas **(CP)** (*see above*). Some features are compared in *Table 21-49*.

RCC usually appear as low-density cystic lesions on CT. One half show capsular enhancement. MRI appearance is variable[404].

Table 21-49 Comparison of craniopharyngioma to Rathke's cleft cyst

Feature	Craniopharyngioma	Rathke's cleft cyst
site of origin	anterior superior margin of pituitary	pars intermedia of pituitary
cell lining	stratified squamous epithelium	single layer cuboidal epithelium
cyst contents	cholesterol crystals	resembles motor oil

surgical treatment	total removal is the goal	partial excision and drainage[404]
cyst wall	thick	thin

21.2.12. Colloid cyst

Key concepts:

- slow-growing benign tumor comprising < 1% of intracranial tumors
- classically occurs in the anterior 3rd ventricle, blocking foramina of Monro → obstructive hydrocephalus involving only the lateral ventricles (≈ pathognomonic)
- enhances minimally or not at all on CT/MRI
- natural history: risk of sudden death has been described, but is controversial
- treatment is surgical. Main options: transcallosal, transcortical/transventricular (only if hydrocephalus), ventriculoscopic

AKA neuroepithelial cysts. Comprise 2% of gliomas, and about 0.5-1% of all intracranial tumors[405]. Usual age of diagnosis: 20-50 yrs.

PATHOGENESIS

Origin: unknown. Implicated structures include: paraphysis (evagination in roof of third ventricle, rudimentary in humans), diencephalic ependyma in the recess of the postvelar arch, ventricular neuroepithelium.

Comprised of a fibrous epithelial-lined wall filled with either mucoid or dense hyloid substance. A slow growing, benign tumor.

Most commonly found in the third ventricle in the region of the foramina of Monro, but may be seen elsewhere, e.g. in septum pellucidum[406].

PRESENTATION

Symptoms are shown in *Table 21-50*. Signs are shown in *Table 21-51*, most commonly presents either with signs of intermittent acute intracranial hypertension (classically attributed to movement of the cyst on its pedicle causing episodic obstruction of the foramina of Monro, rarely born out at operation) or with chronic hydrocephalus (from chronic obstruction). Most clinically significant cysts are > 1.5 cm in diameter.

Table 21-50 Symptoms of colloid cyst at presentation*

Symptom	No.	%
headache	26	68%
gait disturbance	18	47%
disturbed mentation	14	37%
vomiting (± nausea)	14	37%
blurred vision	9	24%
incontinence	5	13%
dizziness	5	13%
tinnitus	5	13%
seizures	4	10%
acute deterioration	4	10%
diplopia	3	8%
"drop attacks"	1	
diabetes insipidus	1	
asymptomatic	1	

* 38 patients, pre-CT era[405]

Sudden death

A high rate of sudden death has been reported with colloid cysts (20% in pre-CT era[407]) but is probably overestimated. The obsolete theory was that these tumors are mobile and thus could shift position and acutely block CSF flow with resultant herniation. Progressive obstruction from tumor growth does often produce chronic hydrocephalus, and it is possible that at some point the brain may decompensate in some cases. Changes in CSF dynamics resulting from procedures (LP, ventriculography…) may have also contributed[408]. Another proposed mechanism is disturbance of hypothalamic-mediated cardiovascular reflex control[408].

Diagnosis

Imaging (MRI or CT) demonstrates the tumor usually located in the anterior 3rd ventricle. Here, it often blocks both foramina of Monro causing almost pathognomonic hydrocephalus involving only the lateral ventricles (sparing the 3rd and 4th).

MRI: usually the optimal imaging technique. However, there are cases where cysts are isointense on MRI and CT is superior[409]. When the lesion is

identifiable, MRI clearly demonstrates the location of the cyst and relation to nearby structures, usually obviating an angiogram. MRI appearance: variable. Usually hyperintense on T1WI, hypointense on T2WI. Enhancement: minimal, sometimes involving only capsule.

CT scan: findings are variable. Most are hyperdense (however, iso- and hypodense colloid cysts occur), and about half enhance slightly. Density may correlate with viscosity of contents, hyperdense cysts were harder to drain percutaneously[410]. CT is usually not quite as good as MRI, especially with isodense cysts. These tumors calcify only rarely.

✖ **LP**: contraindicated prior to placement of shunt due to risk of herniation.

Table 21-51 Signs at presentation*

Sign	No.	%
papilledema	18	47%
gait disturbance	12	32%
normal exam	10	26%
hyperreflexia	9	24%
Babinski reflex	8	21%
incoordination	5	13%
nystagmus	5	13%
tremor	4	10%
hyporeflexia	3	8%
6th nerve palsy	2	5%

* 38 patients with colloid cysts, pre-CT era[405]

TREATMENT

Optimal treatment remains controversial. Initially, shunting without treating the cyst was advocated[411]. The nature of the obstruction (both foramina of Monro) requires bilateral ventricular shunts (or, unilateral shunt with fenestration of the septum pellucidum). Presently, one form or another of direct surgical treatment is usually recommended for some or all of the following reasons:

- to prevent shunt dependency
- to reduce the possibility of tumor progression
- since the mechanism of sudden neurologic deterioration may be due to factors such as cardiovascular instability from hypothalamic compression and not due

to hydrocephalus

Surgical management options (also see *Approaches to the third ventricle*, page 168):

1. transcallosal approaches: not dependent on dilated ventricles. Higher incidence of venous infarction or forniceal injury (*see below*)
2. transcortical approach: higher incidence of post-op seizures (≈ 5%). Not feasible with normal sized ventricles (e.g. in patient with VP shunt) *see page 172*
3. stereotactic drainage: *see below*
4. ventriculoscopic removal: *see below*

Transcallosal approach

Access to the 3rd ventricle via either the foramen of Monro or by interfornicial approach. Since colloid cysts tend to occur exactly at the foramen of Monro, it is rarely necessary to enlarge the foramen to locate the tumor. See *Transcallosal approach to lateral or third ventricle* on page 169.

Stereotactic drainage of colloid cysts

May be useful[412], especially in patients with normal ventricles from shunting, but the contents may be too viscous[413], and the tough capsule may make blind penetration difficult. Total or even subtotal aspiration may not require further treatment in some patients; however, recurrence rate is higher than with surgical removal[414].

Early morbidity was relatively high from this procedure possibly from vascular injury or mechanical trauma; this has improved. May be more feasible with intraoperative ventriculography[415] or with a ventriculoscope[416] (some say this is the initial procedure of choice[417], with craniotomy reserved for treatment failures).

Two features that correlate with unsuccessful stereotactic aspiration[418]:

1. high viscosity: correlates with hyperdensity on CT (low viscosity correlated with hypo- or isodense CT appearance; no MRI finding correlated with viscosity)
2. deflection of the cyst from tip of aspirating needle due to small size

Stereotactic technique[419]:

1. insertion point of stereotactic needle is just anterior to right coronal suture

2. start with sharp-tipped 1.8 mm probe, and advance to 3-5 mm beyond target site (to accommodate for displacement of cyst wall)
3. use a 10 ml syringe and apply 6-8 ml of negative aspiration pressure
4. if this does not yield any material, repeat with a 2.1 mm probe
5. although complete cyst evacuation is desirable, if this cannot be accomplished an acceptable goal of aspiration is re-establishment of patency of the ventricular pathways (may be verified by injecting 1-2 cc of iohexol)

21.2.13. Hemangioblastoma

Key concepts:

- highly vascular well-circumscribed solid or cystic neoplasm of CNS or retina
- the most common primary intra-axial tumor in the adult posterior fossa
- may occur sporadically or as part of von Hippel-Lindau disease
- on imaging, may be solid, or cystic with enhancing mural nodule
- ✔ CBC: may be associated with erythrocytosis (polycythemia)

Hemangioblastomas[267 (p 772-82)] **(HGB)** are histologically benign tumors. Intracranially, they occur almost exclusively in the p-fossa (the most common primary intra-axial pfossa tumor in adults). May occur in cerebellar hemisphere, vermis or brainstem. Less than 100 supratentorial cases have been reported. May also occur in spinal cord (1.5-2.5% of spinal cord tumors) - *see page 732*. Relationship and/or identity with angioblastic meningiomas is controversial. Also difficult to distinguish histologically from a renal cell carcinoma.

HGB may occur sporadically, but 20% occur as part of von Hippel-Lindau disease (*see below*). Retinal HGB and/or angiomas occur in 6% of patients with cerebellar HGBs.

21.2.13.1. von Hippel-Lindau disease (VHL)

Key concepts:

- disorder with hemangioblastomas (HGB) 1° of cerebellum, retina, brainstem & spinal cord, as well as renal cysts/tumors, pheochromocytomas (among others)

- autosomal dominant, due to inactivation of tumor suppressor gene on 3p[25]
- expression and age of onset are variable, but ≈ always manifests by age 60
- mean age of developing HGBs is at least 10 years younger than sporadic HGBs

A multisystem neoplastic disorder characterized by a tendency to develop hemangioblastomas **(HGB)** of the retina, brain and spinal cord, renal clear cell carcinoma **(RCC)**, pheochromocytomas, endolymphatic sac tumors, and others[420, 421] (retinal location is 2nd most common after cerebellar) (*see Table 21-52*). The variability of von Hippel-Lindau disease **(VHL)** has lead some to suggest the use of the term **hemangioblasomatosis**.

Epidemiology

Incidence: 1 in 31,000 to 36,000 live births. ≈ 30% of patients with cerebellar HGB have VHL[10].

Genetics

Autosomal dominant inheritance with ≈ 95% penetrance at age 60 yrs[421, 424]. 4% of VHL are asymptomatic carriers. The VHL gene is a tumor suppressor gene on chromo-some 3p[25], and biallelic inactivation is required for tumor development[10]. Most patients inherit a VHL gene (allele) with the germline mutation from the affected parent and a normal somatic (wild-type) VHL gene from the unaffected parent.

Subtypes of VHL[425]

Type I may have any manifestation of VHL <u>except</u> pheochromocytoma

Type II pheochromocytoma is characteristic

- Type IIA have low risk of renal cell Ca and neuroendocrine pancreatic tumor
- Type IIB higher risk of renal cell Ca and neuroendocrine pancreatic tumor
- Type IIC risk of pheochromocytoma only (without risk of HGB or RCC)

Diagnostic criteria

Suggested diagnostic criteria for VHL:

1. in 80% of patients with VHL there is a multigenerational family history, and only 1 manifestation (CNS HGB or visceral lesion) is necessary to make the diagnosis
2. if no family history (20% of VHL, many of these represent a de novo mutation): 2 manifestations including 1 CNS or retinal HGB are required[426]
3. genetic testing in uncertain cases (*see below*)

Table 21-52 Associations with von Hippel-Lindau disease*

Common lesions	Frequency in VHL
hemangioblastomas	
cerebellum (solid or cystic)	80%
retina	41-59%
brainstem	10-25%
spinal cord	10-50%
pancreatic tumors or cysts	22-80%
renal clear cell Ca & cysts	14-60%
polycythemia	9-20% of intracranial HGBs
Rare lesions (pertinent to nervous system)	**Frequency in VHL**
supratentorial hemangioblastoma	3-6%
cystadenomas of the broad ligament	10% of ♀
papillary cystadenomas of epididymis	25-60% ♂
endolymphatic sac tumors	10-15%
adrenal medullary pheochromocytoma (tends to be bilateral)	7-24%

* see references[421-423] for more

Tumors associated with VHL

1. cerebellar hemangioblastomas **(HGB)**:
   A. prevalence: 44-72% of VHL patients
   B. mean age of diagnosis in patients with cerebellar hemangioblastomas is at least 10 years younger than sporadic cerebellar hemangioblastomas
   C. cysts are commonly associated with cerebellar, brainstem and spinal HGBs

    D. cysts grow at a faster rate than the HGBs, ∴ symptoms related to mass effect are frequently secondary to the cysts
    E. cerebellar HGBs were located in the superficial, posterior and superior half of the cerebellar hemispheres[427]
    F. 93% of the cerebellar HGBs were located in the cerebellar hemispheres and 7% in the vermis
    G. the HGBs are also more frequently found in the superficial posterior half of the brainstem and the spinal cord
    H. the HGBs have multiple sequential growth and quiescent phases
2. spinal cord hemangioblastomas
    A. occur in 13-44% of VHL patients
    B. 90% are located rostrally within the cervical and thoracic cord. Almost all (96%) of the tumors are located in the posterior half of the spinal cord, 4% are located in the ventral half of the spinal cord. 1-3% are found in the lumbosacral nerve roots
    C. by way of comparison, 80% of spinal cord HGB are associated with VHL, whereas only 5-31% of cerebellar HGB are associated with VHL
    D. 95% of symptom-producing spinal HGBs are associated with syringomyelia
3. brainstem hemangioblastomas
    A. usually located in the posterior medulla oblongata usually around the obex and the region within the area prostrema
4. pheochromocytomas **(PCC)**: 20% of PCC are associated with VHL. PCC occur in 7-20% of families with VHL
5. endolymphatic sac tumors **(ELST)**:
    A. locally invasive benign tumors that occur in 10-15% of VHL patients (30% of these will develop bilateral ELSTs - VHL is the only disease with bilateral ELSTs). Rarely metastasize
    B. presents with hearing loss in 95% (may be acute (86%) or insidious (14%)), tinnitus (90%), vertigo or imbalance (66%), aural fullness (30%), and facial paresthesias (8%)
    C. mean age of onset of hearing loss: 22 years (range: 12-50)[428]
6. retinal hemangioblastomas[429]
    A. occur in > 50% of VHL patients. Mean age a presentation: 25 years
    B. frequently bilateral, multifocal and recurrent
    C. often asymptomatic. Visual symptoms occur with progressive growth,

edema, retinal detachments and hard exudates

D. typically located in the periphery and near or on the optic disc

E. microangiomas measuring a few hundred microns without dilated feeding vessels may be located in the periphery

F. retrobulbar HGB are rare(5.3% in NIH cohort)[430]

G. severity of optic disease correlates with CNS and renal involvement

H. early diagnosis and treatment with laser photocoagulation, and cryotherapy can prevent visual loss. Low dose external XRT may be an option for refractory cases

7. renal-cell carcinoma **(RCC)**[423,431-437]
   - A. the most common malignant tumor in VHL. Usually a clear cell carcinoma
   - B. lifetime risk for RCC in VHL: ≈ 70%.
   - C. the growth rate of RCC is high variable
   - D. RCC is the cause of death in 15-50% of patients
   - E. metastases respond poorly to chemotherapy and radiation
   - F. bilateral and multiple lesions are common
   - G. partial nephrectomy or tumor enucleation is preferred to avoid/delay dialysis and transplantation
   - H. nephron- or renal-sparing surgery recommended for tumors less < 3 cm
   - I. promising techniques: cryo- and radiofrequency ablation of tumors < 3 cm
8. renal cysts[423, 433, 436-438]
   - A. 50-70% of VHL patients have bilateral and multiple renal cysts
   - B. rarely cause profound renal impairment
   - C. chronic renal failure or renal hypertension not as common as with polycystic kidney disease
9. epididymal cystadenomas
   - A. benign lesions that arise from the epididymal duct
   - B. found in 10-60% of male VHL patients
   - C. typically appear in the teenage years
   - D. may cause infertility if bilateral
   - E. may be multiple
10. broad ligament cystadenomas
    - A. arise from the embryonic mesonephric duct

B. true incidence unknown

C. rarely reported and usually not recognized in women with VHL

11. pancreatic neuroendocrine tumors and cysts

A. 35 to 70% of patients with VHL develop an endocrine tumor or cyst

B. pancreatic cysts are generally asymptomatic and often multiple

C. pancreatic neuroendocrine tumors are usually non-functional and 8% of them are malignant

D. differential diagnosis: pancreatic islet cell tumors, MEN2

Table 21-53 Health-care provider's surveillance guidelines for patients with or at risk for VHL[*]

Age	Surveillance
Any age	DNA testing for VHL marker is available to identify family members at risk
From birth	check for neurologic deficit, nystagmus, strabismus, white pupil… & refer to retinologist for abnormal findings. Newborn hearing screening
1 year	retina exam[†] (especially if positive for VHL mutation)
2-10 years	**Annual**: • PE[‡] including orthostatic *blood pressure measurement*, neurologic exam, retina exam[†] • blood test or 24° urine for catecholamines & metanephrines (*see page 679*). If elevated: abdominal MRI or MIBG scan (*see page 679*) • abdominal U/S starting at age 8 **Every 2-3 years**: complete audiology exam. Annually if hearing loss, tinnitus or vertigo
11-19 years	**Every 6 months**: retina exam[†] **Annual**: • PE (including scrotal exam in males), neuro exam • 24° urine for catecholamines & metanephrines (*see page 679*). If elevated: abdominal MRI or MIBG scan (*see page 679*) • abdominal U/S (kidneys, pancreas & adrenals). If abnormal: abdominal MRI or CT (except in pregnancy) **Every 1-2 years or if symptoms develop**: • gadolinium MRI of brain & spine. Annually at onset of puberty or before and after pregnancy (only for emergencies during pregnancy) • complete audiology exam. If abnormal, or if tinnitus or vertigo at any time: MRI of IAC to look for ELST
≥ 20 years	**Annual**: • dilated retina exam[†] • PE (including scrotal exam in males), neuro exam • blood test or 24° urine for catecholamines & metanephrines (*see page 679*). If elevated: abdominal MRI or MIBG scan (*see page 679*) • check kidneys, pancreas & adrenals with abdominal U/S and at least every other year unenhanced/enhanced abdominal CT (not during pregnancy) **Every 2 years**: • (or before and after pregnancy, except for emergencies) gadolinium MRI of brain & spine • complete audiology exam. If abnormal, or if tinnitus or vertigo at any time: MRI of IAC to look for ELST
Prior to surgery or childbirth	• blood test or 24° urine for catecholamines & metanephrines (*see page 679*) to rule out pheochromocytoma

* adapted[441]

† indirect ophthalmoscope exam by retinologist familiar with VHL

‡ abbreviations: PE = physical exam by physician familiar with VHL, ELST = endolymphatic sac tumor

Treatment

Resection of individual CNS tumors is usually reserved until symptomatic to decrease the number of operations over a lifetime since the tumors in VHL are usually multiple, tend to recur, and the growth pattern is saltatory. Surgery is the treatment of choice for accessible cystic HGBs. For details, *see page 672* under Hemangioblastoma.

Stereotactic radiosurgery (SRS)[439]): May provide local control rates of > 50% over 5 years. SRS has been recommended for asymptomatic HBG > 5 mm diameter if they are cystic or progressing in size during surveillance[440]. Cranial treatment plan: using a median dose of 22 Gy (range: 12-40Gy) prescribed to the median 82% isodose line in 1-4 sessions. In cystic lesions, treatment is confined to the contrast enhancing mural nodule (the cyst wall is not treated). Spinal treatment plan: median dose of 21 Gy (range 20-25 Gy) prescribed to the median 77% isodose line in 1-3 sessions. Radiosurgery is usually contraindicated in hemangioblastomas with a cyst.

Surveillance

Because of the lifetime risk of developing tumors, regular surveillance is needed. Various protocols have been proposed[442, 443], including those by the NIH[423] and the Danish clinical recommendations[444]. The algorithm recommended by the VHL Family Alliance for patients with VHL and atrisk relatives[A] is shown in *Table 21-53*.

Individuals who do not carry the altered gene on DNA testing do not require surveillance.

Prognosis

The lifespan of patients with VHL is decreased. 30-50% die of renal cell Ca **(RCC)**. Metastases from RCC and neurologic complications from cerebellar HGB are the primary causes of death.

Metastases respond poorly to chemotherapy and XRT.

Resources

Genetic screening for VHL can be done at a few centers. Information for patients and families can be found at www.vhl.org/.

21.2.13.2. Hemangioblastomas (in general)

Epidemiology

HGB represent 1-2.5% of intracranial tumors. Comprise 7-12% of primary p-fossa tumors[445]. 5-30% of cases of cerebellar HGB and 80% of spinal HGB are associated with VHL (*see above*).

A. screening atrisk relatives can be stopped at age 60 years if no abnormalities have been detected

Sporadic cases tend to present in the 4th decade, whereas VHL cases present earlier (peak in 3rd decade). In sporadic cases, the HGB are solitary and originate in the cerebellum (83-95%), spinal cord (3-13%), medulla oblongata (2%)[421] or cerebrum (1.5%)[445]. ≈ 30% of patients with cerebellar HGB have VHL[10].

Presentation

S/S of cerebellar HGB are usually those of any p-fossa mass (H/A, N/V, cerebellar findings… see *Posterior fossa (infratentorial) tumors*, page 590) and obstructive hydrocephalus may occur. HGB is rarely documented as a cause of apoplexy due to intracerebral hemorrhage **(ICH)** (lobar or cerebellar), however, some studies indicate that if cases of ICH are carefully examined, abnormal vessels consistent with HGB (and occasionally misidentified as AVM) may be found with surprising frequency (in spite of negative CT and/or angiography)[446].

Retinal HGBs tend to be located peripherally, and may hemorrhage and cause retinal detachment. Erythrocytosis may be due to erythropoietin liberated by the tumor.

Pathology

No report of malignant change. May spread thru CSF after surgery, but remain benign. No true capsule, but usually well circumscribed (narrow zone of infiltration). May be solid, or cystic with a mural nodule (70% of cerebellar

lesions are cystic; nodules are very vascular, appear red, are often located near pial surface, and may be as small as 2 mm; cyst fluid is clear yellow with high protein). In cystic lesions, the cyst wall is lined with non-neoplastic compressed cerebellum. The cyst develops because the vessel walls are so thin that they leak water, proteins don't cross as readily.

Cardinal feature: numerous capillary channels, lined by a single layer of endothelium, surrounded by reticulin fibers. Macrophages stain PAS positive.

Three types of cells:

1. endothelial
2. pericytes: surrounded by basement membrane
3. stromal: polygonal. Foamy clear cytoplasm, often lipid laden. Origin controversial

Three types of HGB recognized[447]:

1. juvenile: thin walled capillaries & dilated vessels tightly packed
2. transitional: thin walled capillaries & dilated vessels intermingled with stromal cells, some of which are lipid laden (sudanophilic)
3. clear cell: neoplasm made up almost entirely of sheets of xanthoma cells with a rich vascular stroma

Cyst patterns[427]:

1. no associated cysts: 28%
2. peritumoral cyst alone: 51%
3. intratumoral cyst: 17%
4. peritumoral AND intratumoral cysts: 4%

Evaluation

Patients with a p-fossa HGB (radiologically suspected or histologically proven) should undergo MRI of entire neuraxis because of possibility of spinal HGBs (may be distant from p-fossa lesion; may suggest possibility of VHL).

CT: solid lesions are usually isodense with intense contrast enhancement. Cystic HGBs remain low density with contrast, with the nodule enhancing.

MRI: preferable to CT due to the tumor's predilection for the p-fossa. May show serpentine vascular signal voids, especially in the periphery of the lesion. Also, peripheral hemosiderin deposits may occur from previous hemorrhages[445].

Vertebral angiography: usually demonstrates intense vascularity (most other tumors of the p-fossa are relatively avascular). May be required in HGBs

where nodule is too small to be imaged on CT/MRI. 4 patterns: 1) vascular mural nodule on side of avascular cyst, 2) vascular lesion surrounding avascular cyst, 3) solid vascular mass, & 4) multiple, separate vascular nodules.

Labs: often discloses polycythemia (no hematopoietic foci within tumor). In cases with suggestive history, labwork to rule-out catecholamine production from pheochromocytoma may be indicated (see *Endocrine/laboratory studies*, page 681).

TREATMENT

Surgery

Surgical treatment may be curative in cases of sporadic HGB, not in VHL.

Pre-operative embolization may help reduce the vascularity.

Cystic HGBs require removal of mural nodule (otherwise, cyst will recur). The cyst wall is not removed unless there is evidence of tumor within the cyst wall on MRI (typically thick-walled cysts) or visually at the time of surgery[427]. 5-ALA fluorescence may aid in visual localization of small hemangioblastomas within the cyst wall[448].

Solid HGBs tend to be more difficult to remove. They are treated like AVMs (avoid piecemeal removal), working along margin and devascularizing blood supply. A helpful technique is to shrink the tumor by laying a length of bipolar forceps along tumor surface and coagulating. HGBs with attachment to floor of 4th ventricle may be hazardous to remove (cardiorespiratory complications).

Multiple lesions: if ≥ 0.8-1 cm diameter: may treat as in solitary lesion. Smaller and deeper lesions may be difficult to locate at time of surgery.

Radiation treatment

Effectiveness is dubious. May be useful to reduce tumor size or to retard growth, e.g. in patients who are not surgical candidates, for multiple small deep lesions, or for inoperable brainstem HGB. Does not prevent regrowth following subtotal excision.

Chemotherapy

At the time of this writing there is an ongoing phase II trial with sunitnib, an inhibitor of vascular endothelial growth factor and platelet-derived growth factor.

21.2.14. CNS lymphoma

Key concepts:

- may be primary or secondary (pathologically identical)
- suspected with homogeneously enhancing lesion(s) in the central gray matter or corpus callosum (on MRI or CT) especially in AIDS patients
- may present with multiple cranial-nerve palsies
- diagnosis highly likely if tumor seen in conjunction with uveitis
- very responsive initially to steroids (may produce "ghost tumors")
- treatment: usually XRT ± chemotherapy. Role of neurosurgery usually limited to biopsy and/or placement of ventricular access reservoir for chemotherapy

CNS involvement with lymphoma may occur secondarily from a "systemic" lymphoma, or may arise primarily in the CNS. It is controversial whether most intracranial malignant lymphomas are primary[449] or secondary[450].

Secondary CNS lymphoma

Non CNS lymphoma is the fifth most common cause of cancer deaths in the U.S., 63% of new cases are non-Hodgkin's. Secondary CNS involvement usually occurs late in the course. Metastatic spread of systemic lymphoma to the cerebral parenchyma occurs in 1-7% of cases at autopsy[451].

Primary CNS lymphoma

A rare, malignant primary CNS neoplasm comprising 0.85-2% of all primary brain tumors and 0.2-2% of malignant lymphomas[453]. Occasionally metastasizes outside the CNS. Older names include: reticulum cell sarcoma and microglioma[452].

Epidemiology

The incidence of primary CNS lymphoma **(PCNSL)** is rising relative to other brain lesions, and will likely exceed that of low-grade astrocytomas and approach meningiomas. This is in part due to the occurrence of PCNSL in AIDS and transplant patients, but the incidence has also increased in the general population over the past 20 years[454].

Male:female ratio = 1.5:1 (based on literature review[455]).

Median age at diagnosis: 52 yrs[455] (younger among immunocompromised patients: ≈ 34 yrs).

Most common supratentorial locations: frontal lobes, then deep nuclei; periventricular also common. Infratentorially: cerebellum is the most common location.

Conditions with increased risk of primary CNS lymphomas (PCNSL)

1. collagen vascular disease
   A. systemic lupus erythematosus
   B. Sjögren's syndrome: an autoimmune connective tissue disorder
   C. rheumatoid arthritis
2. immunosuppression
   A. chronic immunosuppression in transplantation patients[456]
   B. severe-congenital immunodeficiency syndrome ("SCIDS")
   C. AIDS[457, 458]: CNS lymphoma occurs in ≈ 10% of AIDS patients, and is the first presentation in 0.6%
   D. possibly increased incidence in the elderly due to reduced competency of immune system
3. Epstein-Barr virus[459] is associated with a broad spectrum of lymphoproliferative disorders, and is detectable in ≈ 30-50% of systemic lymphomas, however, it has been associated with almost 100% of PCNSL[460], especially AIDS-related cases[461 (p 317)]

PRESENTATION

Presentation is similar with primary or secondary CNS lymphoma: the two most common manifestations are those due to epidural spinal cord compression and those of carcinomatous meningitis (multiple cranial nerve deficits, see *Carcinomatous meningitis*, page 711). Seizures occur in up to 30% of patients[449].

Symptoms

1. presents with non-focal non-specific symptoms in over 50% of patients; at time of presentation most commonly includes:
   A. mental status changes in one third

    B. symptoms of increased ICP (H/A, N/V)
    C. generalized seizures in 9%
2. focal symptoms in 30-42% of cases:
    A. hemimotor or hemisensory symptoms
    B. partial seizures
    C. multiple cranial-nerve palsies (due to carcinomatous meningitis)
3. combination of focal and non-focal symptoms

Signs

1. non-focal in 16%:
    A. papilledema
    B. encephalopathy
    C. dementia
2. focal findings in 45% of cases:
    A. hemimotor or hemisensory deficits
    B. aphasia
    C. visual field deficits
3. combination of focal and non-focal signs

Uncommon but characteristic syndromes

1. uveocyclitis, coincident with (in 6% of cases) or preceding the diagnosis of (in 11% of cases) lymphoma
2. subacute encephalitis with subependymal infiltration
3. MS-like illness with steroid-induced remission

Pathology

Characteristic sites: corpus callosum, basal ganglia, periventricular.

The neoplastic cells are identical to those of systemic lymphomas. Most are bulky tumors that are contiguous with the ventricles or meninges.

Histologic distinguishing features: tumor cells form cuffs around blood vessels which demonstrate multiplication of basement membranes (best demonstrated with silver reticulum stain).

Frozen section distorts the cells and may lead to a misdiagnosis of malignant glioma[461 (p 320)].

Immunohistochemical stains differentiates B-cell lymphomas from T-cell

lymphomas (B-cell types are more common, especially in PCNSL and in AIDS).

EM shows absence of junctional complexes (desmosomes) that are usually present in epithelial derived tumors.

Intravascular lymphomatosis[462]: Formerly: (malignant) angioendothelomatosis. A rare lymphoma with no solid mass in which malignant lymphoid cells are found in the lumen of small blood vessels in affected organs. CNS involvement is reported in most cases. Presentation is non specific: patients are often febrile, and may present with progressive multifocal cerebrovascular events (including stroke or hemorrhage), spinal cord or nerve root symptoms (including cauda equina syndrome, *see page 446*), encephalopathy or peripheral or cranial neuropathies[463]. Initial transient cerebral symptoms may mimic TIAs or seizures. The ESR is often elevated prior to initiation of steroids. Lymphoma cells may be seen in the CSF.

Painful skin nodules or plaques occur in ≈ 10% of cases, generally involving the abdomen or lower extremities, and these cases may be diagnosed with skin biopsy. Otherwise, diagnosis often requires brain biopsy (open or stereotactic), in which involved areas on imaging studies are targeted. Pathology: malignant lymphoid cells distend and occlude small arteries, veins and capillaries with little or no parenchymal extension[461 (p 324)]. Treatment with combination chemotherapy can result in long-term remission in some patients, but early diagnosis before permanent damage occurs is critical (diagnosis is rarely made pre-mortem).

Diagnosis

On imaging (CT or MRI) 50-60% occur in one or more cerebral lobes (in grey or white matter). 25% occur in deep midline structures (septum pellucidum, basal ganglion, corpus callosum). 25% are infratentorial. 10-30% of patients have multiple lesions at the time of presentation. In contrast, systemic lymphomas that spread to the CNS tend to present with leptomeningeal involvement instead of parenchymal tumors[464].

CT: Non-AIDS-related cases tend to enhance homogeneously, whereas AIDS-related cases often have a necrotic center and appear as multifocal ring-enhancing lesions[465] (the wall is thicker than with an abscess).

Non-AIDS related cases: CNS lymphomas should be suspected with homogeneously enhancing lesion(s) in the central gray or corpus callosum. 75% are in contact with ependymal or meningeal surfaces (this together with dense enhancement may produce a "**pseudomeningioma pattern**", however

lymphomas lack calcifications and tend to be multiple).

60% are hyperdense to brain, only 10% are hypodense. Characteristically, > 90% of these tumors enhance; this is densely homogeneous in over 70%. As a result, when rare non-enhancing cases occur it often leads to a delay in diagnosis[466]. The appearance of enhanced PCNSL on CT has been likened to "fluffy cotton balls". There may be surrounding edema[467] and there is usually mass effect.

There is an almost diagnostic tendency of rapid partial to complete resolution on CT (and even at the time of surgery) following the administration of steroids, earning the nickname of "**ghost-cell tumor**"[468, 469] or disappearing tumor.

MRI: No pathognomonic feature. May be difficult to discern if tumor is located subependymally (signal characteristics similar to CSF); proton-weighted image may avoid this pitfall. Nonenhancing lymphoma (on MRI or CT) is rare[470] (some of these may enhance after XRT) but may be underreported. Bright on DWI (restricted diffusion), isointense to hypointense on ADC map.

CSF: Should only be obtained if no mass effect. Usually abnormal, but non-specific. Most common abnormalities are elevated protein (in > 80%), and increased cell count (in 40%). Cytology is positive for lymphoma cells (pre-operatively) in only 10% (sensitivity may be higher with leptomeningeal involvement as in non-AIDS patients than with parenchymal involvement commonly seen in AIDS). Repeating up to 3 LPs may increase yield.

Angiography: Rarely helpful. 60% of cases show only an avascular mass. 30-40% show diffuse homogeneous staining or blush.

Evaluation

All patients should be assessed (history, physical, and if appropriate, laboratory tests) for any of the conditions associated with lymphoma (*see page 673*). Since primary CNS lymphoma is very rare, any patient with CNS lymphoma should have work-up for occult systemic lymphoma including:

1. careful physical exam of all lymph nodes **(LN)**
2. evaluation of perihilar and pelvic LN (CXR, CT of chest & abdomen)
3. routine blood and urine testing
4. bone marrow biopsy
5. MRI of the entire spine
6. testicular ultrasound in males
7. ophthalmologic examination (including slit-lamp evaluation of both eyes)

in all

A. for possible uveitis

B. ≈ 28% of patients with PCNSL will also have intraocular lymphoma. Often resistant to methotrexate, but responds to low dose ocular XRT (7-8 Gy)

TREATMENT

Surgery

Surgical decompression with partial or gross total removal does not alter patient's prognosis. The main role for surgery is for tumor biopsy, and stereotactic techniques are often well-suited for these often deep tumors[471].

Radiation therapy

The standard treatment after tissue biopsy is whole-brain radiation therapy. Doses used tend to be lower than for other primary brain tumors. ≈ 40-50 Gy total are usually given in 1.8-3 Gy daily fractions.

Chemotherapy

In non-AIDS cases: survival with chemotherapy + XRT is greater than XRT alone[472].

Methotrexate (MTX): The addition of intraventricular MTX (rather than just intrathecal via LP) delivered through a ventricular access device (6 doses of 12 mg twice a week, with IV leucovorin rescue) may result in even better survival[473]. In the event of an intrathecal MTX overdose **(OD)**, interventions recommended[474]: ODs of up to 85 mg can be well tolerated with little sequelae; immediate LP with drainage of CSF can remove a substantial portion of the drug (removing 15 ml of CSF can eliminate ≈ 20-30% of the MTX within 2 hrs of OD). This can be followed by ventriculolumbar perfusion over several hours using 240 ml of warmed isotonic preservative-free saline entering through the ventricular reservoir and exiting through a lumbar subarachnoid catheter. For major OD of > 500 mg, add intrathecal administration of 2,000 U of carboxypeptidase G_2 (an enzyme that inactivates MTX). In cases of MTX OD, systemic toxicity should be prevented by treating with IV dexamethasone and IV (not IT) leucovorin.

Rituximab: Available since 1997 for treatment of refractory systemic B-cell non-Hodgkins lymphoma. Intrathecally, may be more effective for CD33+ lymphomas.

Prognosis

With no treatment, median survival is 1.8-3.3 months following diagnosis.

With radiation therapy[449], median survival is 10 months, with 47% 1-year median survival, and 16% 2-year median survival. 3-year survival is 8%, and 5-year survival is 3-4%. With intraventricular MTX, median time to recurrence was 41 mos[473]. Occasionally, prolonged survival may be seen[475].

About 78% of cases recur, usually ≈ 15 months after treatment (late recurrences also are seen). Of these recurrences, 93% are confined to the CNS (often at another site if the original site responded well), and 7% are elsewhere.

In AIDS-related cases, the prognosis appears worse. Although complete remission occurs in 20-50% following XRT, the median survival is only 3-5 months[476, 477], usually related to AIDS-related opportunistic infection. However, neurologic function and quality of life improve in ≈ 75%[476].

Although there are individual studies that show trends, there are no prognostic features that consistently correlate with survival.

21.2.15. Chordoma

Key concepts:

- primary malignant tumor, usually of clivus or sacrum, with high recurrence rate
- histology: characteristic physaliphorous cells (containing intracellular mucin)
- generally slow-growing and radioresistant
- treatment of choice: wide en bloc resection when possible (piecemeal removal carries risk of inducing metastases), proton-beam radiation may help

Rare tumors (incidence of ≈ 0.51 cases/million) of the remnant of the primitive noto-chord (which normally differentiates into the nucleus pulposus of the intervertebral disks). Can arise anywhere along the neuraxis where there is remnant of notochord, however, cases tend to cluster at the two ends of the primitive notochord: 35% cranially[478] in the spheno-occipital region (clivus),

and 53%[478] in the spine at the sacrococcygeal region[479]. Less commonly, they may occur in the spine above the sacrum[480]. The metastatic rate is low (5-20%)[481], but there is a high recurrence rate of 85% following surgery, and therefore aggressive RTX is usually employed post-op.

PATHOLOGY

Histologically, these tumors are considered low-grade malignancies. However, their behavior is more malignant because of the difficulty of total removal, a high recurrence rate, and the fact that they can metastasize (usually late). They are slow growing, locally aggressive and osteodestructive. Metastases occur in about 10% of sacral tumors, usually late and after multiple resections, and most often to lung, liver and bone. Malignant transformation into fibrosarcoma or malignant fibrous histiocytoma is rare. **Physaliphorous cells** are distinctive, vacuolated cells on histology that probably represent cytoplasmic mucus vacuoles seen ultrastructurally.

RADIOGRAPHIC APPEARANCE

Usually lytic with frequent calcifications[482]. Enhances on CT with contrast[482]. Rarely, may appear as a sclerotic vertebra[483] (“ivory vertebra”).

CRANIAL CHORDOMAS

Peak incidence of cranial chordomas is 50-60 years of age. These tumors are rare in patients < 30 years of age[484]. Male:female distribution is ≈ equal.

Differential diagnosis: Primarily between other cartilaginous tumors of the skull base (for differential diagnosis of other foramen magnum region tumors, *see page 1212*):

1. chondrosarcomas
2. chondromas

Presentation: Usually produces cranial nerve palsies (usually oculomotor or abducens).

SPINAL CHORDOMAS

Occur primarily in the sacrococcygeal region. Unlike cranial chordomas, sacrococcygeal chordomas show a male predominance[478], and these patients tend to be older. May also arise in C2. Chordomas constitute over 50% of primary bone tumors of the sacrum. May produce pain, sphincter disturbance or

nerve root symptoms from local nerve root compression. It may occasionally extend cephalad into the lumbar spinal canal. It is usually confined anteriorly by the presacral fascia, and only rarely invades the wall of the rectum[485]. A firm fixed mass may be palpable between the rectum and the sacrum on rectal exam.

EVALUATION

Characteristic radiographic findings: centrally located destruction of several sacral segments, with an anterior soft-tissue mass that occasionally has small calcifications. CT and MRI show the bony destruction. This is usually difficult to see on plain x-rays. MRI also shows the soft-tissue mass.

Open or CT guided percutaneous posterior biopsy can confirm the diagnosis. Transrectal biopsy should be avoided because of the potential of rectal spread[486].

Chest CT and bone scan: to R/O mets for staging purposes.

TREATMENT

Surgery

Wide en-bloc excision with postoperative radiation is usually the best option, although this may also be only temporarily effective. Decompression is best avoided since entering the mass serves to spread tumor (surgically induced metastases). Chordomas located in C2 are usually not amenable to en bloc resection[487].

Sacral chordomas: The particulars of the surgical procedure are highly dependent on the extent of the lesion. These tumors may spread through the gluteal musculature, and if significant muscular excision is required, then a pedicle based rectus abdominis flap may be employed. A diverting colostomy may be required if it is necessary to resect the rectum or if a cephalic sacral resection is anticipated[488].

For chordomas caudal to the third sacral segment, most agree that a posterior approach is satisfactory. For more rostral lesions, some advocate a combined anterior-posterior approach. However, a posterior approach has been also been used for these[488].

Adverse effects of sacrectomy: if S2 nerve roots are the most caudal nerve roots spared, there is ≈ 50% chance of normal bladder and bowel control[488]. If S1 or more cephalic roots are the most caudad nerve roots spared, most will have impaired bladder control and bowel problems[488].

Radiation therapy (XRT)

Best results were obtained with en bloc excision (even if marginal), sometimes combined with high-dose XRT[480, 489] (conventional XRT did not prevent recurrence when incorporated with palliative or debulking surgery[480]), but it did lengthen the interval to recurrence[489]). Early radiation was associated with longer survival[490]. Higher XRT doses can be used in the sacrococcygeal region (4500-8000 rads) than in the cervical spine (4500-5500 rads) because of concerns of radiation injury to the spinal cord. IMRT and stereotactic radiosurgery have also been used[487].

Proton beam therapy, alone[481] or combined with high-energy x-ray (photon) therapy[491, 492] may be more effective than conventional XRT alone. However, proton beam therapy requires travel to one of a very limited number of facilities with a cyclotron (in the U.S.: Boston, or Loma Linda, California) which may be difficult to arrange for what is typically ≈ 7 weeks of fractionated treatments.

Chemotherapy

Imatinib (Gleevec®) (a tyrosine kinase inhibitor) has some antitumor effect in chordoma[493].

Outcome

Median survival is 6.3 years[487].

21.2.16. Ganglioglioma

Key concepts:

> • composed of two cell types: ganglion cells (neurons) and glial cells
> • extremely rare (< 2% of intracranial neoplasms)
> • seen primarily in the first 3 decades of life
> • characterized by slow growth and a tendency to calcify

A tumor composed of two types of cells: ganglion cells (neurons) which may arise from primitive neuroblasts, and glial cells, usually astrocytic in any phase of differentiation[494].

Epidemiology

Location: May occur in various parts of the nervous system (cerebral hemispheres, spinal cord, brainstem, cerebellum, pineal region, thalamus, intrasellar, optic nerve, and peripheral nerve have been reported[495]). Most occur above the tentorium, primarily in or near the 3rd ventricle, in the hypothalamus or in the temporal or frontal lobes[142]. Brain-stem gangliogliomas occur rarely (*see page 607*).

Incidence: Typically quoted[495] as 0.3-0.6%. One series[496] found gangliogliomas in 1.3% of all brain tumors (including mets), or 3% of *primary* brain tumors. Considering only children and young adults, incidence ranges from 1.2-7.6% of brain tumors[495].

Demographics: Occurs primarily in children and young adults (peak age of occurrence: 11 yrs).

Presentation

Most common presenting symptom was seizure, or a change in a pre-existing seizure pattern. Often, the seizures are difficult to control medically.

Radiologic evaluation

Neuroradiologic findings are not specific for this tumor.

Plain skull x-ray: calcification was noted in 2 of 6 patients[495].

CT: all of 10 patients had a low density lesion on non-contrast CT; 8 enhanced slightly with contrast; 5 of the 10 had calcification on CT[496]. 6 of the 10 were in temporal lobe (this predilection has been noted in many but not all series), and 4 were in frontal lobe. Frequently appears cystic on CT, but still may be found to be solid at operation. Mass effect rare (suggests slow growth).

MRI: high signal on T1WI, low signal on T2WI. Calcifications appear as low signal on both[495].

Angiography: shows either an avascular or a minimally vascular mass.

Pathology

Mixture of 2 types of neoplastic cells: neuronal (ganglion) and astrocytic (glial). Very slow growing.

Two major classifications: **ganglioneuromas** (less common, more benign; predominance of neuronal component) and **gangliogliomas** (preponderance of glial cells).

Grossly: white matter mass; well-circumscribed, firm, with occasional cystic areas and calcified regions. Most dissect easily from brain, but the solid portion may show an infiltrative tendency[495].

Microscopically: ganglion cells must demonstrate nerve cell differentiation, e.g. Nissl substance and axons or dendrites. Pitfall: differentiating neoplastic neurons from neurons entrapped by an invading astrocytoma may be difficult. Also, neoplastic astrocytes may resemble neurons on light microscopy. 2 of 10 patients had areas of oligodendroglioma. One series found necrotic areas in 7 of 14 patients, minimal calcification, and Rosenthal bodies[497]. Suggested criteria for diagnosis[498]:

1. clusters of large cells potentially representing neurons (required for diagnosis)
2. no perineural clustering of glial cells around the suspected neoplastic neurons
3. fibrosis (desmoplasia)
4. calcification

Aggressive malignant changes in the glial component may dictate a poor outcome, although an "aggressive" background is not unusual and may not indicate malignancy.

Treatment

Recommendation is wide radical excision when possible (may be more limited in spinal cord and brainstem tumors). Close follow-up is recommended, and re-resection should be considered for recurrence. The role of XRT is unknown, and due to the deleterious effects together with the good long-term prognosis, it is not recommended initially but may be considered for recurrence[499].

Prognosis

Russell and Rubinstein[500] first proposed that the grade of the astrocytic component of the tumor determines the prognosis. This has been supported by some case reports, but clinical series have not been able to correlate histology with outcome[499]. Thus, anaplasia is not significantly associated with a worse prognosis[499].

The majority of patients did well and were asymptomatic after resection. 1 patient in a series of 10 died 3 days post-op from cerebral edema.

In 58 patients, 5-year survival was 89% and 10-year survival was 84%[499]. In

9 brainstem gangliogliomas, 5-year survival was 78%.

The value of radiation therapy is not known. Consider radiation when growth is evident on follow-up CT, or when infiltration is felt to occur at time of surgery.

1 patient had degeneration to glioblastoma when a recurrence was discovered 5 years after removal (this patient received radiation therapy).

The prognosis with following subtotal resection of brainstem gangliogliomas is better than for brainstem gliomas as a group[142].

21.2.17. Paraganglioma

AKA **chemodectoma**, AKA **glomus tumors**. *Table 21-54* shows the designation of these tumors in various sites.

These tumors arise from paraganglion cells (not chemoreceptor cells as previously thought, therefore the term *chemodectoma* is losing favor). Slow growing tumors (< 2 cm in 5 years).

Histologically benign (< 10% associated with lymph node involvement or distant spread). Most contain secretory granules on EM (mostly epinephrine & nor-epinephrine, and these tumors may occasionally secrete these catecholamines with risk of life-threatening HTN and/or cardiac arrhythmias).

Table 21-54 Designation based on site of origin

Site	Designation
carotid bifurcation (most common)	carotid body tumors
auricular branch of vagus (middle ear)	glomus tympanicum
superior vagal ganglion (jugular foramen)	glomus jugulare
inferior vagal (nodose) ganglion (nasopharynx at skull base) (least common)	glomus intravagale (AKA glomus vagale)
adrenal medulla & sympathetic chain	pheochromocytoma

Glomus tumors may occur in 2 patterns:

1. familial: non multicentric. Up to 50%
2. nonfamilial. may be multicentric (metachronous) 5%

PHEOCHROMOCYTOMA

Located in the adrenal gland. May be sporadic, or as part of familial

syndrome (von Hippel-Lindau disease - *see page 667*, MEN 2A & 2B, & neurofibromatosis). Consider genetic testing if age at diagnosis is < 50 years for mutations of VHL and other genetic abnormalities.

Laboratory studies

1. fractionated plasma metanephrines: 96% sensitivity, 85% specificity[501]. More sensitive than serum catecholamines with sporadic elevations. Pheochromocytoma is ruled out if plasma normetanephrine **(NMN)** < 112 pg/ml and metanephrine **(MN)** < 61 pg/ml. Highly suspicious if NMN > 400 pg/ml or MN > 236 pg/ml
2. 24 hr urine collection for: total catecholamines (epinephrine and norepinephrine) and metanephrines (88% sensitivity, 99.7% specificity[502])
3. where elevation is found, a clonidine suppression test can be done. Normal response consists of a fall in plasma catecholamines to ≤ 50% of baseline and below 500 pg/ml (there will be a reduction in essential hypertension, but no change with pheochromocytoma or other tumor production)

Imaging

Indicated when laboratory tests confirm pheochromocytoma.

MRI with contrast is preferred over CT.

CT may be used when MRI is contraindicated, but is less sensitive, especially for lesions < 1 cm diameter.

123I MIBG (iodine-123-meta-iodobenzylguanidine) scintigraphy detects extra-adrenal pheochromocytomas with 83-100% sensitivity, 95-100% specificity. If not available 131I MIBG may be used with 77-90% sensitivity, 95-100% specificity.

CAROTID BODY TUMORS

Possibly the most common paraganglioma (pheochromocytoma may be more common). Approximately 5% are bilateral; the incidence of bilaterality increases to 26% in familial cases (these are probably autosomal dominant).

CLINICAL

Usually present as painless, slow growing mass in upper neck. Large tumors may → cranial nerve involvement (especially vagus and hypoglossal). May also cause stenosis of ICA → TIAs or stroke.

EVALUATION

1. carotid angiogram: demonstrates predominant blood supply (usually external carotid, with possible contributions from vertebral and thyrocervical trunk). May also detect bilateral lesions. Characteristic finding: splaying of bifurcation
2. MRI (or CT): evaluates extent, and assesses for intracranial extension

TREATMENT

Resection reported to carry a high complication rate, including stroke (8-20%) and cranial nerve injury (33-44%). Mortality rate is 5-13%.

GLOMUS TUMORS

Glomus tumors may be subdivided into *glomus jugulare* and *glomus tympanicum* tumors. Glomus jugulare tumors arise from the jugular bulb (in the jugular foramen at the junction of the sigmoid sinus and jugular vein). Glomus tympanicum tumors are centered higher than glomus jugulare. Glomus tumors are rare (0.6% of all head and neck tumors), yet the glomus tympanicum is the most common neoplasm of the middle ear. Glomus jugulare tumors **(GJT)** arise from glomus bodies, usually in the area of the jugular bulb, and track along vessels. May have finger-like extension into the jugular vein (which may embolize during resection)[503]. Most are slow growing, although rapidly growing tumors do occur.

Vascular supply: very vascular. Main feeders of GJT are from the external carotid (especially inferior tympanic branch of ascending pharyngeal artery, and branches of posterior auricular, occipital, and internal maxillary), with additional feeders from petrous portion of the ICA. Glomus tympanicum tumors feed from the auricular artery.

CLINICAL

Epidemiology

Female:male ratio is 6:1. Bilateral occurrence is almost nonexistent.

Symptoms

Patients commonly present with hearing loss and pulsatile tinnitus. Dizziness

is the third most common symptoms. Ear pain may also occur.

Signs

Hearing loss may be conductive (e.g. due to obstruction of the ear canal) or sensorineural due to invasion of the labyrinth often with accompanying vertigo (the eighth nerve is the most common cranial nerve involved). Various combinations of palsies of cranial nerves IX, X, XI & XII occur (see *Jugular foramen syndromes*, page 115) with occasional VII palsy (usually from involvement within the temporal bone). Ataxia and/or hydrocephalus can occur with massive lesions that cause brainstem compression. Occasionally patients may present with symptoms due to secretory products (*see below*).

Otoscopic exam → pulsatile reddish-blue mass behind eardrum (occasionally, lamentably biopsied by ENT physician with possible ensuing massive blood loss).

PATHOLOGY

Histologically indistinguishable from carotid body tumors. May invade locally, both through temporal bone destruction and especially along pre-existing pathways (along vessels, eustachian tube, jugular vein, carotid artery). Intradural extension is rare. Malignancy may occur, but is rare. These tumors rarely metastasize.

Secretory properties

These tumors usually possess secretory granules (even the functionally inactive tumors) and may actively secrete catecholamines (similar to pheochromocytomas, occurs in only 1-4% of GJT[504]). Norepinephrine will be elevated in functionally active tumors since glomus tumors lack the methyltransferase needed to convert this to epinephrine. Alternatively, serotonin and kallikrein may be released, and may produce a carcinoid-like syndrome (bronchoconstriction, abdominal pain and explosive diarrhea, violent H/A, cutaneous flushing, hypertension, hepatomegaly and hyperglycemia)[505]. During surgical manipulation, these tumors may also release histamine and bradykinin, causing hypotension and bronchoconstriction[506].

DIFFERENTIAL DIAGNOSIS

See *Cerebellopontine angle (CPA) lesions* on page 1210. The major differential is neurilemmomas (vestibular schwannomas), both enhance on CT. A

cystic component and extrinsic compression of the jugular bulb are characteristic of neurilemmomas. Angiography will differentiate difficult cases.

EVALUATION

Neurophysiologic testing

Audiometric and vestibular testing should be performed.

Imaging

1. CT or MRI used to delineate location and extent of tumor; CT is better for assessing bony involvement of the skull base
2. angiography: confirms diagnosis (helping to rule out vestibular schwannoma), and ascertains patency of contralateral jugular vein in event that jugular on side of tumor must be sacrificed; jugular bulb and/or vein are usually partially or completely occluded

Endocrine/laboratory studies

(*see page 679*)

CLASSIFICATION

A number of classification schemes have been proposed. The modified Jackson classification is shown in *Table 21-55*.

Table 21-55 Modified Jackson classification[507]

Type	Description	Intracranial extension
I	small; involves jugular bulb, middle ear & mastoid	none
II	extends under IAC	possible
III	extends into petrous apex	possible
IV	extends beyond petrous apex into clivus or infratemporal fossa	possible

TREATMENT

Surgical resection is usually simple and effective for small tumors confined to the middle ear. For larger tumors that invade and destroy bone, the relative role of surgery and/or radiation is not fully determined. With large tumors, surgery carries the risk of significant cranial nerve palsies.

Medical

For tumors that actively secrete catecholamines, medical therapy is useful for palliation or as adjunctive treatment before embolization or surgery. Alpha and beta blockers given before embolization or surgery blocks possibly lethal blood pressure lability and arrhythmias. Adequate blockade takes ≈ 2-3 weeks of alpha blocker and at least 24 hours of beta blocker therapy; in emergency, 3 days of treatment may suffice.

Alpha blockers

Reduce BP by preventing peripheral vasoconstriction.

- **phenoxybenzamine** (Dibenzyline®): long acting; peak effect 1-2 hrs. Start with 10 mg PO BID and gradually increase to 40-100 mg per day divided BID
- **phentolamine** (Regitine®): short acting. Usually used IV for hypertensive crisis during surgery or embolization.

Rx: 5 mg IV/IM (peds: 1 mg) 1-2 hrs pre-op, repeat PRN before and during surgery

Beta blockers

Reduces catecholamine induced tachycardia and arrhythmias (may also prevent hypotension that might occur if only alpha blockade is used). These drugs are not always needed, but when used ✖ NB: these drugs must not be started before starting alpha-blockers (to prevent hypertensive crisis and myocardial ischemia).

- **propranolol** (Inderal®): ***Rx***: oral dose is 5-10 mg q 6 hrs. IV dose for use during surgery is 0.5-2 mg slow IVP
- **labetalol** (Normodyne®): may have some efficacy in blocking α_1 selective and ß non-selective (potency < propranolol), *see page 20*

Serotonin, bradykinin, histamine release blockers

These agents may provoke bronchoconstriction that does not respond to steroids, but may respond to inhaled ß-agonists or inhaled anticholinergics. Somatostatin may be used to inhibit release of serotonin, bradykinin, or histamines. Since this drug has a short half-life, it is preferable to give octreotide 100 µg sub-Q q 8 hrs (*see page 653*).

Radiation therapy

XRT may relieve symptoms and stop growth in spite of persistence of tumor mass. 40-45 Gy in fractions of 2 Gy has been recommended[508]. Lower doses of ≈ 35 Gy in 15 fractions of 2.35 Gy appear as effective and have fewer side effects[509]. Generally used as primary treatment only for large tumors or in patients too elderly or infirmed to undergo surgery. Some surgeons pretreat 4-6 mos pre-operatively with XRT to decrease vascularity[510] (controversial).

Embolization

- generally reserved for large tumors with favorable blood supply (i.e. vessels that can be selectively embolized with no danger of particles passing thru to normal brain)
- post-embolization tumor swelling may compress brainstem or cerebellum
- may be used preoperatively to reduce vascularity. Performed 24-48 hours pre-op (not used prior to that, because of post-embolization edema)
- caution with actively secreting tumors which may release vasoactive substances (e.g. epinephrine) upon infarction from the embolization
- may also be used as primary treatment (± radiation) in patients who are not surgical candidates. In this case, is only palliative, as tumor will develop new blood supply
- absorbable (Gelfoam®) and non-absorbable (Ivalon®) materials have been used

Surgical treatment

The tumor is primarily extradural, with extremely vascular surrounding dura.

Suboccipital approach may cause dangerous bleeding and usually results in incomplete resection. Team approach by a neurosurgeon in conjunction with a neuro-otologist and possibly head and neck surgeon has been advocated[377]. This approach utilizes an approach to the skull base through the neck.

ECA feeders are ligated early, followed rapidly by draining veins (to prevent systemic release of catecholamines).

Sacrifice of the jugular vein **(JV)** is tolerated if the contralateral JV is patent (often, the ipsilateral JV will already be occluded).

Complications and outcome

The most common complications are CSF fistula, facial nerve palsy, and

varying degrees of dysphagia (from dysfunction of lower cranial nerves). Dysfunction of any of the cranial nerves VII thru XII can occur, and a tracheostomy should be performed if there is any doubt of lower nerve function, and a gastrostomy feeding tube may be needed temporarily or permanently. Lower cranial nerve dysfunction also predisposes to aspiration, the risk of which is also increased by impaired gastric emptying and ileus that may occur due to reduced cholecystokinin **(CCK)** levels post-op. Excessive blood loss can also occur.

Even after gross total tumor removal, recurrence rate may be as high as one third[510, 511].

21.2.18. Ependymoma

Ependymomas arise from ependymal cells lining the cerebral ventricles and the central canal of the spinal cord. They may occur anywhere along the neuraxis, in pediatrics they are most common in the posterior fossa (*see below*), in adults they tend to be intraspinal (*see page 730*).

Epidemiology:

- intracranial: comprises only ≈ 5-6% of intracranial gliomas, 69% occur in children[512], comprise 9% of pediatric brain tumors[513]. Incidence of pediatric intracranial ependymomas: ≈ 200 cases/yr in the U.S.
- spinal: ≈ 60% of spinal cord gliomas, 96% occur in adults[512], especially those of filum terminale (see *myxopapillary ependymoma* below)

Ependymomas have the potential to spread via the CSF through the neuraxis, a process known as “seeding”, resulting in so-called “drop mets” in 11%. The incidence is higher with higher grade[513]. Systemic spread occurs on rare occasion.

The mean age at diagnosis is shown in *Table 21-56*.

Table 21-56 Mean age at diagnosis of ependymoma[512]

Location (in 101 patients)	All patients (yrs)	Children (yrs) (age < 15 yrs)
intracranial	17.5	5
infratentorial	14.5	4.5
supratentorial	22	6.5
intraspinal	40	
intramedullary	47	

cauda region	32	

PATHOLOGY

Although they are usually circumscribed with a covering layer of ependyma, ependymomas may be invasive.

Classification is a work in progress. Ependymomas from different locations (pfossa, supratentorial, spinal cord) are genetically distinct[514]. The World Health Organization **(WHO)** classification of ependymal tumors:

1. ependymoma (WHO II) - variants:
   A. cellular
   B. papillary: "classic lesion" occurring in brain or spinal cord. Can metastasize in up to 30% of cases. Dark, small nuclei. 2 cytoplasmic patterns:
      1. differentiation along glial line: these form **perivascular pseudorosettes** (areas of radiating processes lacking nuclei surrounding blood vessels) which, when they occur, are diagnostic
      2. cuboidal cells: these form **true rosettes** (ependymal tubules around a central blood vessel)
   C. clear cell
   D. tanycytic: rare. Tumor cells appear similar to "ependymoglia" or "tanycytes" (stretched cells present to a limited degree in the normal CNS). True rosettes are absent. No preference for age, sex or location within CNS2. Treatment of choice: gross total resection[2]
2. **myxopapillary ependymoma**: (WHO I) distinctive, occurs only in filum terminale. Papillary, with microcystic vacuoles and mucosubstance (*see page 731*)
3. **subependymomas**: (WHO I) typically occur in anterior lateral ventricles or posterior fourth ventricle, with prominent role of subependymal glial cells. Classically do not enhance (*see page 1226*). Not uncommon at autopsy, rarely surgical
4. anaplastic ependymomas: (WHO III) pleomorphism, multinucleation, giant cells, mitotic figures, vascular changes and areas of necrosis (the term **ependymoblastoma** has occasionally been used for more anaplastic lesions, but this term is best reserved for a distinct, rare childhood primitive neuroectodermal tumor, *see page 688*). It is unclear if the degree of anaplasia has any effect on outcome

INTRACRANIAL EPENDYMOMAS

Key concepts:

- usually benign tumors, often fibrillary with epithelial appearance. Perivascular pseudorosettes or true rosettes may be seen in classic (papillary) form
- most often occur in the floor of the 4th ventricle, presenting with hydrocephalus (increased ICP) and cranial nerve VI & VII palsies
- evaluation: includes imaging the entire neuraxis (usually with enhanced MRI: cervical, thoracic, lumbar & brain) because of potential for seeding through CSF
- worse prognosis the younger the patient (especially age < 24 months)
- treatment: the best outcomes are associated with gross total removal (no enhancing tumor on post-op MRI) followed by XRT. XRT may be withheld for age < 3
- do LP ≈ 2 weeks post op to send ≈ 10 cc of CSF for cytology for prognostication

Usually well circumscribed and benign (although anaplastic (malignant) ependymomas do occur), commonly arises in the floor of the fourth ventricle (60-70% are infratentorial, all of these occur near 4th ventricle[512], they comprise 25% of tumors in region of 4th ventricle[515 (p 2792)]). Children with p-fossa ependymomas often have anaplastic tumors with a higher risk of spread through the neuraxis. Supratentorial ependymomas are often cystic. Rarely occur outside the CNS in: mediastinum, lung or ovaries. Although not as malignant histologically as medulloblastomas, ependymomas have a worse prognosis due to their propensity to invade the obex which precludes complete removal.

CLINICAL

Symptoms

Mostly those of posterior fossa mass with increased ICP[515 (p 2795)] (from hydrocephalus) and cranial nerve involvement.

Symptoms of increased ICP:

1. headache: 80%
2. N/V: 75%

3. ataxia or vertigo: 60%
4. seizures: only in ≈ 30% of supratentorial lesions; comprise only 1% of patients with intracranial tumors presenting with seizures

Cranial nerve involvement: invasion of the floor of the 4th ventricle may involve the facial colliculus producing facial nerve palsy (involvement of internal genu of VII, *see page 844*) and abducens palsy (from VI nucleus).

EVALUATION

MRI: imaging study of choice. Image the entire craniospinal axis with and without contrast because of possibility of drop mets. Usually appears as a mass in the floor of fourth ventricle, often with obstructive hydrocephalus. May be difficult to distinguish from medulloblastoma **(MBS)** radiographically, *see page 1210* for differentiating features.

CT: not as detailed for evaluation of posterior fossa.

Myelogram: water-soluble contrast myelography is about as sensitive as gadolinium enhanced MRI in detecting "drop mets". Myelography also provides CSF for cytology for staging.

MICROSCOPIC FEATURES

See *Pathology* on page 683.

TREATMENT

Surgical resection

Goal of surgery: maximal possible resection of intracranial portion without causing neurological deficits. Gross total resection may not possible when invasion of the floor is extensive, or when tumor extends through the foramen of Lushka (bradycardia may prevent GTR).

2 weeks postoperatively, perform LP to look for "drop mets": 10 cc of CSF is sent for cytology to quantitate (if any) number of malignant cells (may be used to follow treatment). If LP is positive, then by definition there are drop mets. If negative, it is not as helpful (sensitivity is not high). CSF from an EVD is not as sensitive as LP.

Lesions in fourth ventricle region are approached via midline suboccipital craniectomy.

Radiation therapy (XRT)

Ependymomas rank 2nd only to medulloblastomas in radiosensitivity. XRT is administered after surgical excision (survival is improved with post-op XRT: 50% survival time was 2 yrs longer with XRT than without[512], and 5-year survival increased from 20-40% without XRT to 40-80% with XRT[516]), however, for patients age < 3 years, *see below*.

1. cranial XRT
   A. traditional therapy: 45-48 Gy to tumor bed[516] (recurrence treated with additional 15-20 Gy)[515 (p 2797)]
   B. recent recommendations: 3-D conformal XRT with higher doses (59.4 Gy delivered to tumor bed + 1 cm margins)[517]
   C. intensity modulated proton beam therapy appears equivalent in terms of local control, but may be better at sparing normal tissue[518]
2. spinal XRT: most radiate only if drop mets or if positive CSF cytology (however, prophylactic spinal is controversial[519])
   A. low dose XRT to entire spinal axis (median dose = 30 Gy[516])
   B. boost to any regions showing drop mets
3. XRT is undesirable in age < 3 due to side effects. XRT was avoided in ≈ 30% of patients < 3 years age with comparable survival when XRT was reserved for treatment failures[520, 521]. This concept of selective XRT may be applicable to older children as well[522]

Chemotherapy

Role is very limited.

1. has little impact on newly diagnosed cases. Adjuvant chemo after XRT in patients > 3 years showed no benefit
2. may reduce vascularity of ependymomas which may facilitate GTR (sometimes in a second stage operation)
3. may be considered for infants < ≈ 3 years age to delay use of XRT (*see above*)
4. chemo at the time of recurrence may arrest tumor progression for short periods

OUTCOME

Operative mortality[515 (p 2797)]: 20-50% in early series; more recently: 5-8%.

Operative morbidity: advise patients/families pre-op of the likelihood need for post-op gastric feeding tube (G-tube) and tracheostomy (these may be temporary).

Age: peds vs. adults: 5-year survival is 20-30% in the pediatric group[513, 523], compared with up to 80% in adults. Patients 24-35 months old did better (5-year survival = 73%) than those younger than 24 months (26% 5-YS) or those older than 36 months (36% 5-YS)[524].

Pathology: prognosis is worse with anaplastic ependymoma (WHO III) than with "standard" grade (WHO II)[525, 526]. However, excluding WHO III tumors, malignant features in an ependymoma do not necessarily portend a worse prognosis[527].

Extent of resection: the risk of recurrence is highest following subtotal resection. Gross total resection **(GTR)** (surgical) of primary intracranial tumor followed by craniospinal XRT as outlined above yields 41% 5-year survival.

Treatment failure: WHO Grade II tumors tend to recur initially at the site of origin[525]. However, primary failure in 9-25% of patients is via **drop mets**[524, 528].

SPINAL EPENDYMOMAS

The most common spinal cord glioma below the mid-thoracic region.

See *Intramedullary spinal cord tumors* on page 730.

21.2.19. Embryonal tumors

A few words about PNETs

Initially, the term primitive neuroectodermal tumor **(PNET)** encompassed a wide variety of previously individually named tumors which all seemed to share certain pathologic features suggesting origin from a common progenitor cell in the subependymal matrix (primitive neuroectodermal cells) (although the actual cell of origin is unknown). They are histologically indistinguishable but genetically distinct[529]. Now, the recommendation is to call these "embryonal tumors"[5], but the term PNET is entrenched. These tumors include: retinoblastoma, pineoblastoma, neuroblastoma, esthesioneuroblastoma. Medulloblastoma **(MB)** is more than just a PNET of the posterior fossa (*see below*), as alterations involved in evolution of MBs such as beta-catenin and APC mutations are absent in pineoblastomas and supratentorial primitive PNETs

(sPNETs). At least some MBs originate from the external granular layer **(EGL)** of the cerebellum.

Embryonal tumors

Location: Embryonal tumors most commonly arise in the cerebellar vermis (medulloblastoma), but also occur in cerebrum, pineal, brainstem or spinal cord. Primary spinal cord PNETs are extremely rare (approximately 30 cases reported by 2007530). sP-NETS have a worse prognosis than MB (*see below*).

Dissemination: Embryonal tumors **(ETs)** may disseminate via the CSF spontaneously[531], or iatrogenically (following surgery or shunting, the latter is a rare cause of tumor dissemination[25]). Thus, all patients with ETs require spinal axis evaluation (gadolinium enhanced MRI is about as sensitive as water-soluble myelography) and cytologic examination of CSF. Prophylactic craniospinal XRT is indicated following surgical removal, but cranial XRT is avoided if at all possible before 3 years of age to avoid intellectual impairment and growth retardation (see *Radiation injury and necrosis*, page 771). Extraneural metastases can also occur.

21.2.19.1. Supratentorial primitive neuroectodermal tumors

Supratentorial primitive neuroectodermal tumor **(sPNETs)** are highly malignant lesions primarily affecting young children (65% occur in age < 5 years) and account for 2.5–6% of childhood brain tumors. Occur rarely in adults. No gender predilection. Histologically indistinguishable from medulloblastoma **(MB)**, they have a distinct genetic pro-file, are more aggressive, and often respond poorly to MB-specific therapies (especially pineoblastomas). Overall survival rate for sPNETs is substantially lower than that for MBs, with an expected 3- year progression-free survival of approximately 50% for localized supratentorial PNETs[532, 533].

21.2.19.2. Medulloblastoma (MB)

Key concepts:

- a small-cell embryonal tumor of the cerebellum found predominantly in children (peak: 1st decade). The most common pediatric brain malignancy
- usually arises in the cerebellar vermis in the region of the apex of the roof of the 4th ventricle (fastigium), often producing hydrocephalus

- brainstem invasion usually limits complete surgical excision
- all patients must be evaluated for “drop mets”

Epidemiology

In children: MBs comprise 15-20% of intracranial tumors[138], 30-55% of p-fossa tumors. MB is the most common malignant pediatric brain tumor[534]. MBs comprise < 1% of adult brain neoplasms. Peak incidence: during 1st decade. Median age at diagnosis: 5-7 years (75% are diagnosed by age 15). Male:female ratio is 2:1. Familial cancer syndromes that include MB: Gorlin syndrome, Turcot syndrome (*see page 588*).

Clinical

Clinical history is typically brief (6-12 weeks). MBs usually arise in the cerebellar vermis, at the apex of the roof of the 4th ventricle (fastigium in the region of the posterior medullary velum), which predisposes to early obstructive hydrocephalus. Usual presenting symptoms: H/A, N/V, and truncal & appendicular ataxia. Infants with hydrocephalus may present with irritability, lethargy, or progressive macrocrania[535]. Spinal drop mets may produce back pain, urinary retention or leg weakness. Common signs: papilledema, ataxia, nystagmus, EOM palsies.

Seeding & metastases

≈ 10-35% have seeded the cranio-spinal axis at the time of diagnosis[138], and extra-neural mets occur in 5% of patients[534], sometimes promoted by shunting[536] (although this is uncommon[25]).

Evaluation

Usually appears as a solid, IV-contrast-enhancing lesion on CT or MRI (however, a rare diffuse variant in children < 3 yrs, medulloblastoma with extensive nodularity[44] **(MBEN)**, has been described). Most are located in the midline in the region of the 4th ventricle (laterally situated tumors are more common in adults). Most have hydrocephalus. Ependymoma is the main entity to differentiate from on imaging (*see page 1210*.

CT: noncontrast → typically hyperdense (due to high cellularity), contrast → most enhance. 20% have calcifications.

MRI: T1WI → hypo- to isointense. T2WI → heterogeneous due to tumor cysts, vessels and calcifications[537]. Most enhance (including MBEN)

Spinal imaging: MRI with IV gadolinium or CT/myelography with water-soluble contrast should be done to rule-out "drop mets". Staging is done either pre-op or within 2-3 weeks of surgery.

Pathology

All MB are WHO grade IV[538].

Histologic subtypes[538]:

1. classic (90%): small, densely packed undifferentiated cells with hyperchromatic nuclei, scant cytoplasm (and inconstant cell clusters in Homer-Wright rosettes)[537] (sometimes called "blue tumor") (monotonous appearance)
2. desmoplastic (6%): similar to classic type with "glomeruli" AKA pale islands (collagen bundles and scattered, less cellular areas). Marked tendency for neuronal differentiation. More common in adults. Prognosis controversial: may be the same[539] or less aggressive[2] than classic MB
3. large cell (4%[540]): large, round, and/or pleomorphic nucleoli, higher mitotic activity. In the few case reports, all were male. More aggressive than classic. Resembles atypical teratoid/rhabdoid tumors of cerebellum, but has different phenotype and cytogenic features

Molecular biology

The molecular genetic alterations in MBs can be divided into 3 groups:

1. non-random chromosomal abnormalities: (e.g. consistent deletion of 17p markers) has been shown in 35–40%
2. information from gene profiling:
   A. ZIC and NSCL1 were the genes most closely correlated with MBs
   B. certain genes were associated with more favorable outcome[529]
3. abnormalities in signal transduction pathways: e.g. neurotrophin signaling pathway (important in cerebellar development) or Sonic hedgehog (Shh)[541]

Treatment

Stratification of patients into risk groups guides therapy (*see Table 21-57* below).

MB are highly radiosensitive and moderately chemosensitive.

Treatment of choice: surgical debulking of as much tumor as possible (without causing neurological injury) followed by craniospinal XRT (radiation is necessary because of propensity to recur and to seed). Invasion of or attachment to the floor of the fourth ventricle (brainstem in the region of the facial colliculus) often limits excision. It is better to leave a small residual on the brain-stem (these patients do fairly well) than it is to chase every last remnant into the brain-stem (neurologic deficit is more likely with this).

Surgical exposure of midline cerebellar medulloblastomas requires opening of the foramen magnum, usually removal of the posterior arch of C1, and occasionally the arch of C2. Tumor spread with arachnoidal thickening (“sugar coating”) may occur.

XRT: optimal irradiation dose: 35-40 Gy to whole craniospinal axis + 10-15 Gy boost to tumor bed (usually posterior-fossa) and to any spinal mets seen, all fractionated over 6-7 wks[542, 543]. Reduce dosages by 20-25% for age < 3 yrs, or use chemotherapy instead. Lower dose radiation (25 Gy) to the neuraxis may provide acceptable control when confirmed gross total excision is achieved[544].

Chemotherapy: there is no standardized chemotherapy regimen. Lomustine (CCNU), cisplatin and vincristine (VCR) are primarily used, but are usually reserved for recurrence, for poor risk patients (see *Prognosis* below), or for children < 3 yrs age. Significant survival advantage was shown in poor-risk children with adjuvant chemotherapy (5-year actuarial disease-free survival rate = 87%) compared to those without (33%). No difference was observed among standard-risk patients[545].

Shunts: 30-40% of children require permanent VP shunts following p-fossa resection. The risk of shunt-related seeding has been quoted as high as 10-20%[138], but this is probably overestimated[25]. In the past, tumor filters were frequently used. They are less commonly used today because of the high incidence of obstruction.

Table 21-57 Risk stratification in medulloblastoma

Standard-risk patients
No residual tumor on post-op MRI and negative CSF results. 5-year survival is > 5%, and progression-free survival = 50%[546, 547]
Poor-risk patients
Bulky residual tumor > 1.5 cm^2 post-op and dissemination in the brain, spine or CSF. Worse prognosis. 5-year disease-free survival is 35-50%[548]
Intermediate risk patients

An intermediate risk group probably exists, but has been poorly characterized

Prognosis

Poor prognosticators[549]

- younger age (especially if < 3 yrs)
- disseminated (metastatic) disease
- inability to perform gross-total removal (especially if residual > 1.5 cm^2 in patient with localized disease)
- histological differentiation along glial, ependymal, or neuronal lines

One stratification scheme is shown in *Table 21-57*.

The sex of the child is an important predictor for survival of MB; girls had a much better outcome[550]. Gene expression profiling is highly predictive of response to therapy, predicting outcome with much greater accuracy than current staging criteria[529]. The ability of multiple biological and clinical markers to predict outcomes for patients with MB is currently under investigation[551, 552].

Long-term survivors of MB are at significant risk for permanent endocrinologic, cognitive, and psychological sequelae of treatments. Infants and very young children with MB remain a difficult therapeutic challenge because they have the most virulent form of the disease and are at highest risk for treatment-related sequelae.

Most common site of recurrence is p-fossa.

21.2.19.3. Ependymoblastoma

A highly cellular embryonal form of ependymal tumor[553]. Occurs most often in age < 5 yrs. Prognosis is poor, with median post-op survival ranging from 12-20 months, and almost 100% mortality rate at 3 yrs. As with other tumors in this category, there is a tendency for subarachnoid seeding.

21.2.19.4. Atypical teratoid/rhabdoid tumors (AT/RT)

A unique embryonal tumor of the CNS. Many of these tumors were probably previously misdiagnosed as MBs. Occurs primarily in infants and children (> 90% are < 5 years of age, with most age < 2 years). A minority are associated with primary renal rhabdoid tumor. 50% of AT/RTs occur in posterior fossa with a predilection for the cerebellopontine angle **(CPA)**.

33% have CSF spread at presentation. Most patients die within 1 year of

diagnosis.

Histopathology: some tumors are composed entirely of rhabdoid cells, others have a combination of rhabdoid and areas resembling PNET/MB. Other cell types include: malignant mesenchymal cells (usually spindle cells), malignant epithelial cells (glandular or squamous).

Molecular biology: AT/RT and the rhabdoid renal tumors have a deletion or monosomy of chromosome 22.

21.2.20. Epidermoid and dermoid tumors

AKA epidermoid or dermoid *cysts*.

Table 21-58 Comparison of epidermoids and dermoid

Feature	Epidermoid	Dermoid
frequency	0.5-1.5% of brain tumors	0.3% of brain tumors
lining	stratified squamous epithelium	also include dermal appendage organs (hair follicles and sebaceous glands)
contents	keratin, cellular debris, and cholesterol, occasional hair	same as epidermoids, plus hair and sebum
location	more common laterally (e.g. CP angle)	more commonly near midline
associated anomalies	tend to be isolated lesions	associated with other congenital anomalies in up to 50% of cases
meningitis	may have recurrent aseptic meningitis (including Mollarets meningitis, *page 690*)	may have repeated bouts of bacterial meningitis

Comparison of dermoids and epidermoids

Both are usually developmental, benign tumors that may arise when retained ectodermal implants are trapped by two fusing ectodermal surfaces. The growth rate of these tumors is linear, like skin (rather than exponential, as with neoplastic tumors). Distinguishing features between the two tumors are shown in *Table 21-58*. They may occur in the following locations

1. calvaria: skull involvement occurs when ectodermal rests are included in the developing cranium (*see page 699*), epidural extension may occur with growth
2. intracranial: the most common sites include
   A. suprasellar: commonly produce bitemporal hemianopsia and optic atrophy, and only occasionally pituitary (endocrine) symptoms

(including DI)

B. sylvian fissure: may present with seizures

C. CPA: may produce trigeminal neuralgia, especially in young patient

D. basilar-posterior fossa: may produce lower cranial nerve findings, cerebellar dysfunction, and/or corticospinal tract abnormalities

E. within the ventricular system: occur within the 4th ventricle more commonly than any other

3. scalp
4. within the spinal canal:
   A. most arise in the thoracic or upper lumbar spine
   B. epidermoids of the lower lumbar spine may occur iatrogenically following LP (see *Lumbar puncture*, page 201)
   C. dermoids of the spinal canal are usually associated with a dermal sinus tract (*see page 252*) and may produce recurrent bouts of spinal meningitis

EPIDERMOID CYSTS

Key concepts:

- usually arise from ectoderm trapped within or displaced into the CNS
- predilection for: CP angle, 4th ventricle, suprasellar region, spinal cord
- sometimes AKA cholesteatoma (not to be confused with cholesterol granuloma)
- grow at linear rate (unlike exponential rate of true neoplasms)
- imaging: CSF-like mass (hisignal on DWMRI is the best test to differentiate)
- may produce aseptic meningitis (Mollaret's meningitis is one form)
- treatment: surgical excision. XRT has no role

AKA **cholesteatoma** (not cholesterol *granuloma* (*see below*)), AKA pearly tumor, AKA ectodermal inclusion cyst (*see Table 21-58* above for comparison to dermoids). Although epidermoids and cholesteatomas are histologically identical (both arise from epithelium entrapped in an abnormal location, epidermoids are intradural, cholesteatomas are extradural), the term cholesteatoma is most often used to describe the lesion in the middle ear where the entrapped epithelium usually arises from chronic middle ear infections which lead to a retraction pocket (rarely, may instead be congenital).

May arise from any of the following[554]:

1. displaced dorsal midline ectodermal cell rests trapped during neural tube closure between gestational weeks 3-5
2. multipotential embryonic cell rests
3. epithelial cell rests carried to the CPA with the developing otic vesicle
4. epidermal cells displaced into CNS, e.g. by LP (see *Lumbar puncture*, page 201) or repeated percutaneous cranial subdural taps[555]

EPIDEMIOLOGY

Epidermoids comprise 1% of intracranial tumors[556], and ≈ 7% of CPA tumors. Peak age of occurrence: 40 years. No gender difference.

HISTOLOGY

Epidermoids are lined by stratified squamous epithelium, and contain keratin (from desquamated epithelium), cellular debris, and cholesterol[557]. Growth occurs at a linear rate like normal skin, unlike the exponential growth of true neoplasms[558]. The cyst contents may be liquid or may have a flaky consistency. They tend to spread along normal cleavage planes and surround vital structures (cranial nerves, ICA…). Bony destruction occurs in a minority, usually with larger tumors. Rare degeneration to squamous cell cancer[559] primarily in cases of repeated recurrences after multiple surgeries.

Distinction from cholesterol granuloma

Epidermoid cysts are sometimes mistakenly equated with cholesterol granulomas[560], possibly because of the similarity between the terms cholesteatoma and cholesterol granuloma. However, these are distinct lesions[561]. Cholesterol granulomas usually occur following chronic inflammation (usually in pneumatized portions of the temporal bone: petrous apex, mastoid air cells, middle ear space). Some differences are delineated in *Table 21-59*.

PRESENTATION

1. may present as any mass lesion in the same location
2. CPA lesions can produce V, VII or VIII neuropathies
3. recurrent episodes of aseptic meningitis caused by rupture of the cyst contents, which may also lead to hydrocephalus. Symptoms include fever and meningeal irritation. CSF shows pleocytosis, hypoglycorrhachia,

elevated protein, and negative cultures. Cholesterol crystals may be seen and can be recognized by their amorphous birefringent appearance. **Mollaret's meningitis** is a rare variant of aseptic meningitis which includes the finding of large cells in the CSF that resemble endothelial cells (which may be macrophages[564]) that may be seen in some patients with epidermoid cysts[565, 566]

Table 21-59 Characteristics of epidermoid & cholesteatoma vs. cholesterol granuloma

Feature	Epidermoid	Cholesteatoma	Cholesterol granuloma
origin	ectodermal cells in abnormal location		chronic inflammatory cells surrounding cholesterol crystals (? from break-down of RBC membranes)
	(within CNS, intradural)	(within ear, extradural)	
precursor	usually congenital, occasionally acquired (e.g. after LP, *see page 203*)	usually acquired (following chronic infection ? due to epithelial cells from tympanic membrane), occasionally congenital	chronic middle ear infection or idiopathic hemotympanum
symptoms	vary depending on location	chronic hearing loss, ear drainage, pain or numbness around ear	usually involve vestibular or cochlear dysfunction
imaging (may not reliably distinguish among these)	CT: low density; no enhancement; bone erosion in only 33% MRI: T1WI: intensity slightly > CSF; T2WI: tumor & CSF similar hi intensity		CT: homogeneous & isodense; rim enhancement; extensive destruction of petrous bone MRI: increased signal on both T1WI and T2WI
gross appearance	pearly white		brown (from hemosiderin)
microscopic pathology[562]	hyperkeratotic cyst lined with stratified squamous epithelium		fibroblastic proliferation, hemosiderin-laden macrophages, cholesterol clefts, giant cell reaction
ideal treatment	aggressive near-total excision		subtotal resection followed by drainage & restoration of pneumatization[563]

IMAGING

MRI: (*see Figure 21-4*) mimics CSF on T1WI (low signal, may be slightly > CSF) and T2WI (high signal). Tumors are usually also high signal on T2WI, but most enhance with contrast on T1WI (epidermoids do not enhance). An epidermoid may pass from the posterior fossa through the incisura to the middle fossa.

Diffusion weighted imaging **(DWI)** is the best test to differentiate

epidermoids from CSF (e.g. as in similar appearing arachnoid cyst). Epidermoids show intense signal on DWI as a result of restriction of water movement.

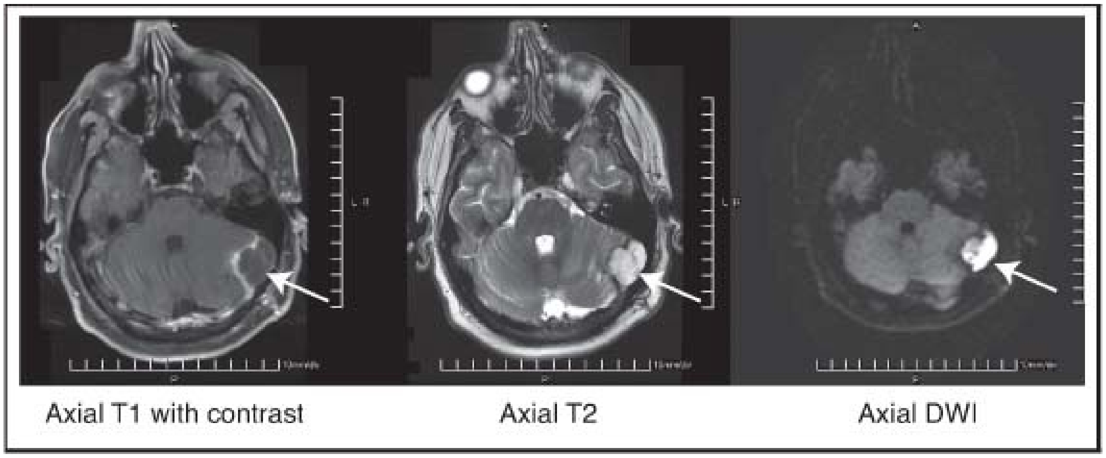

Figure 21-4 MRI demonstrating left cerebellopontine angle epidermoid Note that the CSF is dark on the DWI

CT: low density, slightly greater than CSF. No enhancement[567] (enhancement suggests a possible malignant epithelial component). Bone erosion is seen in 33%.

Treatment

Caution when removing epidermoid cysts to minimize spilling contents as they are quite irritating and may cause severe chemical meningitis (Mollaret's meningitis, *see above*). Berger[554] advocates intraoperative irrigation with hydrocortisone (100 mg/L of LR) to reduce the risk of post-op communicating hydrocephalus. Peri-operative IV steroids and copious saline irrigation during surgery may provide similar results. The tumor is cyst wall, and the surgical plan is generally to remove as much as possible but to leave capsule adherent to critical structures such as brainstem and blood vessels as the morbidity of removal is high and, a small residual is does not preclude satisfactory out-come.

In spite of adequate removal, it is not unusual to see persistent brainstem distortion on post-op imaging[561]. Post-op radiation is not indicated as the tumor is benign and XRT does not prevent recurrence[568].

21.2.21. Pineal region tumors

Key concepts:

- wide variety of pathology: germ cell tumors (mostly germinomas, teratomas), astrocytomas, & pineal tumors (mostly pineoblastomas) account for most tumors
- since tumors may be of mixed cell types, CSF tumor markers (ß-hCG, AFP…) are not as useful for diagnosis as they are for following response to treatment
- traditionally a test dose of XRT was employed, but there is a growing trend to obtain tissue diagnosis in all cases if possible before instituting treatment

Pineal region[569]: bounded dorsally by the splenium of the corpus callosum and the tela choroidea, ventrally by the quadrigeminal plate and midbrain tectum, rostrally by the posterior aspect of the 3rd ventricle, and caudally by the cerebellar vermis.

A striking feature is the diversity of lesions (neoplastic and nonneo-plastic) that may occur in this location due to the variety of tissues and conditions normally present, as shown in *Table 21-60*.

Table 21-60 Conditions giving rise to pineal region tumors

Substrate in pineal region	Tumor that may arise
pineal glandular tissue	pineocytomas and pineoblastomas
glial cells	astrocytomas (including pilocytic), oligodendrogliomas, glial cysts (AKA pineal cyst)
arachnoid cells	meningiomas, arachnoid cysts (non-neoplastic). Meningiomas characteristically displace the internal cerebral vein inferiorly
ependymal lining	ependymomas
sympathetic nerves	chemodectomas
rests of germ cells	germ cell tumors: choriocarcinoma, germinoma, embryonal carcinoma, endodermal sinus tumor (yolk sac tumor), and teratoma
absence of blood-brain barrier (BBB) in pineal gland	makes it a susceptible site for hematogenous metastases
remnants of ectoderm	epidermoid or dermoid cysts
Non neoplastic lesions that may mimic tumors	
vascular	vein of Galen aneurysm (*page 1112*), AVM
infectious	cysticercosis (*page 370*)

PINEAL CYSTS (PCS)

Usually an incidental finding (i.e. not symptomatic), seen on ≈ 4% of MRIs[570] or on 25-40% of autopsies[571] (many are microscopic). The most common ones are intra-pineal glial-lined cysts with diameter < 1 cm. Etiology is obscure, PCs are nonneoplastic, and may be due to ischemic glial degeneration or due to sequestration of the pineal diverticulum. They have been regarded as benign, but the natural history is not known with certainty[572]. PCs may contain clear, slightly xanthochromic, or hemorrhagic fluid. Rarely, they may enlarge, and like other pineal region masses, may become symptomatic by causing hydrocephalus by aqueductal compression[573], gaze paresis[574] including Parinaud's syndrome (*see page 114*), or hypothalamic symptoms.

Positional H/As have been attributed to PCs, the theory is that the cyst could intermittently compress the vein of Galen and/or sylvian aqueduct[575]. This remains unproven since asymptomatic compression of the vein of Galen and the quadrigeminal plate has been demonstrated on MRI[576].

Imaging

May escape detection on CT because the cyst fluid density is often similar to CSF. MRI T1WI shows round or ovoid abnormality in region of pineal recess, signal varies with protein content (isointense or slightly hyperintense). T2WI occasionally show increased intensity[572]. Gadolinium occasionally enhances the cyst wall with a maximum thickness of 2 mm; irregularities of the wall with nodular enhancement suggests the lesion is not benign.

Epidermoid-dermoid cysts may also occur in the pineal region, and are larger and have different signal characteristics on MRI.

Management

Asymptomatic PCs < 2 cm diameter with typical appearance should be followed clinically and with annual imaging studies. Surgery to relieve symptoms or to obtain a diagnosis is suggested for symptomatic lesions or for ones that show changes on MRI.

Surgery options for patients with hydrocephalus:

1. CSF shunt: may not relieve gaze disturbance (from pressure on tectal plate)
2. cyst excision: relieves symptoms and establishes diagnosis. Low morbidity

3. stereotactic or endoscopic aspiration: may not get enough tissue for diagnosis
4. endoscopic third ventriculostomy **(ETV)** (*see page 212*): useful only for typical PC as it does not obtain tissue for pathology. A few cases of regression of PCs after ETV have been reported[577]

PINEAL REGION NEOPLASMS

Tumors in this region are more common in children (3-8% of pediatric brain tumors) than in adults (≤ 1%)[578]. Over 17 tumor types occur in this region[579]. Germinoma is the most common tumor (21-44% in American/European population, 43-70% in Japan), followed by astrocytoma, teratoma and pineoblastoma[580]. Many tumors are of mixed cell type.

Germ cell tumors **(GCT)**, ependymomas and pineal cell tumors metastasize easily through the CSF ("drop metastases").

PINEAL GLAND TUMORS

Pineal cell tumors

A **pineocytoma** (AKA pinealcytoma) is a well differentiated neoplasm arising from pineal epithelium. **Pineoblastoma** (AKA pinealblastoma) is a malignant tumor that is considered a primitive neuroectodermal tumor **(PNET)** (*see page 686*). Both can metastasize through the CSF, and both are radiosensitive.

Germ cell tumors (GCT)

When they arise in the CNS, GCTs occur in the midline in the suprasellar and/or pineal region (simultaneous suprasellar and pineal region lesions is diagnostic of a GCT, so-called **synchronous germ cell tumors**, comprise 13% of GCTs, and are highly sensitive to XRT[581]). In the pineal region, these tumors occur predominantly in males. In females, GCTs are more common in the suprasellar region[582]. Aside from benign teratomas, all intracranial GCTs are malignant and may metastasize via CSF and systemically. Types of GCTs:

1. germinomas: malignant tumors of primitive germ cells that occur in the gonads (called testicular seminomas in males, dysgerminomas in females) or in the CNS. Survival with these is much better than with nongerminomatous tumors

2. non-germinomatous germ cell tumors **(NGGCT)** include:
   A. embryonal carcinoma
   B. choriocarcinoma
   C. endodermal sinus tumor **(EST)** AKA yolk sac carcinoma: usually malignant
   D. teratoma
      1. mature
      2. immature

Tumor markers

GCTs characteristically (but not always) give rise to tumor markers in the CSF (see *Tumor markers used clinically*, page 721).

Elevated CSF beta-human chorionic gonadotropin **(ß-hCG)** is classically associated with choriocarcinomas, but also occurs with up to 50% of germinomas (which are more common).

Alpha-fetoprotein **(AFP)** is elevated with endodermal sinus tumors, embryonal carcinoma and occasionally with teratomas. Elevated placental alkaline phosphatase **(PLAP)** in serum or CSF occurs with intracranial germinomas[583]. *Table 21-61* summarizes these findings. When positive, tumor markers can be followed serially to assess treatment and to look for recurrence (they should be checked in serum and CSF). NB: tumor markers alone are not usually sufficient for making a definitive diagnosis of a pineal region tumor since many of these tumors are mixed cell type.

Table 21-61 Occurrence of CSF tumor markers with pineal germ cell tumors*

Tumor	ß-hCG†	AFP	PLAP‡
choriocarcinoma	≈ 100%	–	–
germinoma	10-50%	–	+
embryonal carcinoma	–	+	–
yolk sac carcinoma	–	+	–
immature teratoma	–	+	–
mature teratoma	–	–	–

* adapted with permission from personal communication, Ashraf Samy Youssef, M.D., Ph.D.
† abbreviations: ß-hCG = beta human chorionic gonadotropin, AFP = alpha-fetoprotein, PLAP = placental alkaline phosphatase
‡ elevated PLAP may also occur in serum

A breakdown of pediatric pineal region tumors in one series is shown in *Table 21-62* (series A).

In 36 patients < 18 yrs age, 17 distinct histological tumor types were identified: 11 germinomas (the most common tumor), 7 astrocytomas, and the remaining 18 had 15 different tumors[584].

Adult

GCTs and pineal cell tumors occur primarily in childhood and young adults. Thus, over the age of 40, a pi-neal region tumor is more likely to be a meningioma or a glioma. Series B in *Table 21-62* includes both adult and pediatric patients.

Clinical

Almost all patients have hydrocephalus by the time of presentation, causing typical signs and symptoms of headache, vomiting, lethargy, memory disturbance, abnormally increasing head circumference in infants, and seizures. Parinaud's syndrome (or the syndrome of the sylvian aqueduct) may be present (*see page 114*). Precocious puberty may occur only in boys with choriocarcinomas or germinomas with syncytiotrophoblastic cells, due to leuteinizing hormone-like effects of ß-hCG secreted in the CSF. Suprasellar GCT: triad of diabetes insipidus, visual deficit and panhypopituitarism[582].

Drop metastases from CSF seeding can produce radiculopathy and/or myelopathy.

Table 21-62 Pineal region tumors

Tumor	Series A* (%)	Series B† (%)
germinoma	30	27
astrocytoma	19	26
pineocytoma	6	12
malignant teratoma	6	
unidentified germ-cell tumor	6	
choriocarcinoma	3	1.1
malignant teratoma/embryonal cell tumor	3	1.6
glioblastoma	3	
teratoma	3	4.3
germinoma/ectodermal sinus tumor	3	

dermoid	3	
embryonal cell tumor	3	
pineoblastoma	3	12
pineocytoma/pineoblastoma	3	
endodermal sinus tumor	3	
glial cyst (pineal cyst)[585]	3	2.7
arachnoid cyst	3	
metastases		2.7
meningioma		2.7
ependymoma		4.3
oligodendrogliomas		0.54
ganglioglioneuroma		2.7
lymphoma		2.7

* 36 children ≤ 18 yrs[584]

† 370 tumors in patients 3-73 yrs old[578]

Management

The optimal management strategy for pineal region tumors has yet to be determined. **“Test dose” radiation:** Controversial. This is giving way to the doctrine of obtaining histology in most cases (e.g. by stereotactic biopsy) because of the harmful effects of XRT and because 36-50% of pineal tumors are benign or radioresistant[586]. The concept was that if a pineal region tumor enhanced uniformly and had the classic appearance of a germinoma on MRI, a test dose of 5 Gy was given, and if the tumor would shrink then the diagnosis of germinoma was virtually certain and XRT was continued without surgery. This may needlessly expose a patient with benign or radioresistant tumors to XRT, 578. “Trial XRT” should be avoided in tumors suspected of being teratomas or epidermoid cyst on MRI, and the response may be misleading in the relatively common situation of tumors with mixed cell types.

Management suggestions

1. get MRI of cervical, thoracic and lumbar spine to assess for drop mets
2. send for GCT markers (ß-hCG, AFP, PLAP (*see page 692*)) (somewhat helpful, but not adequate for diagnosis)[A]:
   A. serum

B. CSF (if able to safely obtain[B])

3. obtain histology in most cases. Most often this involves a biopsy, which should be generous (to avoid missing other histologies in mixed cell tumors)
   A. if hydrocephalus: transventricular biopsy
   B. if no hydrocephalus:
      1. open biopsy or
      2. stereotactic biopsy or
      3. ? by CACE (*see below*)
4. based on markers and histology:
   A. germinoma: XRT + chemo
   B. all other tumors: one option is resection followed by adjuvant therapy (usually not very helpful) - see *Indications:*, page 695 for controversies

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A. if negative (–) for GCT markers, it may be a pineal cell tumor, or it may be a GCT without markers (see *Tumor markers*, page 692). If positive, it can still be a mixed cell-type tumor

B. LP is contraindicated with large intracranial mass and/or obstructive hydrocephalus; CSF may be obtained from EVD if placed

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Hydrocephalus

Patients presenting acutely due to hydrocephalus may be best treated with external ventricular drainage **(EVD)**. This permits control over the amount of CSF drained, prevents peritoneal seeding with tumor (a rare event[25]), and may avoid having a permanent shunt placed in the significant number of patients who will not need one after tumor removal (although ≈ 90% of patients with a pineal GCT require a shunt). Ventricular access (via EVD or Frazier burr hole, *see page 156*) in the post-op period is important in the event of acute hydrocephalus.

Stereotactic procedures

May be used to ascertain diagnosis (biopsy), or to treat symptomatic pineal region cysts[587, 588]. Caution is advised since the pineal region has numerous vessels (vein of Galen, basal veins of Rosenthal, internal cerebral veins, posterior medial choroidal artery)[589] which may be displaced from their normal position. The complication rate of stereotactic biopsy is: ≈ 1.3% mortality, ≈ 7% morbidity, and 1 case of seeding in 370 patients, and the diagnostic rate is ≈

94%[578]. A shortcoming of stereotactic biopsy is that it may fail to disclose the histologic heterogeneity of some tumors.

Two main stereotactic trajectories: 1) anterolateral (low frontal) approach below the internal cerebral veins, and 2) posterolateral trans-parieto-occipital[579]. One study found that the trajectory correlated with complications, and they recommended the anterolateral approach[590]. However, the correlation of trajectory and complications was not born out in another study[578], and they found that the complication rate was higher in firm tumors (pineocytomas, teratomas, and astrocytomas) and they recommend an open approach when the tumor appears difficult to penetrate on the first attempt at biopsy.

Stereotactic radiosurgery may be appropriate for treatment of some lesions.

Computer-assisted cisternal endoscopic approach (CACE)

Employs a supracerebellar infratentorial approach that permits visualization of neurovascular structures and avoids traversing brain parenchyma[579].

Radiation treatment

For controversies regarding "test dose" XRT, see *Management*, page 693. Germinomas are very sensitive to radiation (and chemotherapy), and are probably best treated with these modalities and followed.

XRT is also utilized post-op for other malignant tumors. For highly malignant tumors or if there is evidence of CSF seeding, craniospinal XRT with a boost to the tumor bed is appropriate.

If possible, XRT is best avoided in the young child (*see page 771*). Chemotherapy may be used for age < 3 yrs until the child is older when XRT is better tolerated[582].

Surgical treatment of the tumor

Indications: Controversial. Some authors feel that most tumors (except germinomas, which are best treated with XRT) are amenable to open resection[591]. Others feel that resection should be limited to ≈ 25% of tumors which are[578]:

1. radioresistant (e.g. malignant nongerminoma GCTs): 35-50% of pineal region tumors (larger numbers occur in series not limited to pediatric

patients)
2. benign (e.g. meningioma, teratomas…)
3. well encapsulated
4. NB: malignant germ cell tumors should be without evidence of metastases (those with metastases do not benefit from surgery on the primary tumor)
5. pineocytoma: recommendation is for surgical excision + SRS for any residual

Options:
1. direct surgery: obtains generous tissue for biopsy. Curative for benign lesions. Not the optimum treatment for malignant tumors and germinomas without complications
2. biopsy followed by adjuvant therapy: the preferred management for malignancies and germinomatous germ cell tumors

Surgical approaches: Choice is aided by the pre-op MRI and includes:
1. most common approach: midline infratentorial-supracerebellar approach of Horsley and Krause as refined by Stein[592]. Cannot be used if the angle of the tentorium is too steep (best assessed on MRI). May be done in the sitting position (risk of air embolism, *see page 153*) or in the Concorde position (*see page 153*)
2. occipital transtentorial: wide view. Risk of injury to occipital visual cortex or splenium of corpus callosum. Recommended for lesions centered at or superior to the tentorial edge or located above the vein of Galen or for rare cysts with superior extension. The occipital lobe is retracted laterally, and the tentorium is incised 1 cm lateral to the straight sinus
3. transventricular: indicated for large, eccentric lesions with ventricular dilatation. Usually via a cortical incision in the posterior portion of the superior temporal gyrus. Risks: visual defect, seizures, and on dominant side language dysfunction
4. lateral paramedian infratentorial
5. transcallosal: largely abandoned except for tumors extending into corpus callosum and third ventricle
6. paramedian infratentorial-supracerebellar approach may be used for cysts that do not extend superiorly or contralaterally[572]: avoids midline venous structures

Important surgical considerations:

The base of the pineal gland is the posterior wall of the 3rd ventricle. The

splenium of the corpus callosum lies above, and the thalamus surrounds both sides. The pineal projects posteriorly and inferiorly into the quadrigeminal cistern. The deep cerebral veins are a major obstacle to operations in this region. Venous drainage of the pineal region must be preserved.

Surgical outcome:

Mortality rate: 5-10%[578]. Postoperative complications include: new visual field deficits, epidural fluid collection, infection, and cerebellar ataxia.

21.2.22. Choroid plexus tumors

Most are histologically benign (**choroid plexus papilloma (CPP)**, WHO I), although intermediate (atypical choroid plexus papilloma, WHO II) and malignant tumors (**choroid plexus carcinoma (CPC)**, WHO III) may occur. Malignant degeneration from WHO I or II to grade III was seen in 2 out of 124 patients with 59 months mean follow-up[593]. All may produce drop mets in the CSF, but WHO III do so more commonly. Although usually slow growing, they sometimes grow rapidly.

Atypical CPP have more mitotic figures than CPP without frank signs of malignancy seen in CPC[594], and up to 2 of the following 4 features may be observed: increased cellularity, nuclear pleomorphism, blurring of the papillary pattern, areas of necrosis.

Epidemiology

Prevalence: 0.4-1% of all intracranial tumors. 1.5-6% of tumors in peds.

Although they may occur at any age, 70% of patients are < 2 yrs old[595]. Some tumors occur in neonates, supporting the hypothesis that some of these are congenital[596].

Location: in adults these tumors are usually infratentorial, whereas in children they tend to occur supratentorially (a reverse from the situation for most other tumors) in the lateral ventricle[596] with a predilection for the left side. See *Intraventricular lesions* on page 1224 for differential diagnosis. They can be located anywhere there is choroid plexus, with the most frequent locations: the lateral or fourth ventricles, the CPA (from extension of choroid plexus through the foramen of Luschka).

Presentation

Most present with symptoms of increased ICP from hydrocephalus (H/A, N/V, craniomegaly), others may present with seizures, subarachnoid hemorrhage (with meningismus), or focal neurologic deficit (hemiparesis, sensory deficits, cerebellar signs, or cranial nerve palsies of III, IV and VI).

Hydrocephalus, which may result from: overproduction of CSF (although total removal of these tumors does not always cure the hydrocephalus - especially in patients with high CSF protein, hemorrhage from tumor or surgery, or ependymitis), obstruction of CSF outflow, or communicating hydrocephalus from CSF borne particulates.

Imaging

Brain MRI or CT without and with contrast usually demonstrates a densely enhancing multilobulated intraventricular mass classically with projecting "fronds". Hydrocephalus is common.

Treatment

There is no role for chemotherapy or radiation for WHO I lesions. For choroid plexus carcinoma, chemotherapy benefits a subset of patients[597].

Surgical treatment:

Benign lesions may be cured surgically with total removal, and even the malignant tumors respond well to surgery. The operation may be difficult due to fragility of the tumor and bleeding from the choroidal arteries. However, persistence with a second and sometimes even third operation is recommended as 5-year survival rate of 84% can be achieved[596]. Post-operative subdural collections after transcortical tumor excision may occur, and may result from a persistent ventriculosubdural fistula, which may require subdural-peritoneal shunting[595].

Recurrence

12 recurrences (6% of WHO I and 29% of WHO II patients) requiring neurosurgical intervention occurred in 124 complete resections with 59 months mean follow-up[593].

21.2.23. Glial tumors of uncertain origin

1. astroblastoma
2. chordoid glioma of the 3rd ventricle[598]: rare, benign tumor of adulthood. Solid, enhancing mass of the 3rd ventricle. Female:male ratio = 3:1. Mitotic activity is absent in most tumors. GFAP immunostaining is common, S100 reactivity is variable. Histologically similar appearing to chordoid meningioma, which lacks GFAP staining. Attachment to wall of 3rd ventricle (hypothalamus) may prevent total removal

21.2.24. Tumors of peripheral nerves

PERINEURIOMA

A nerve sheath tumor. Variants:

1. intraneural perineurioma: usually solitary lesion of adolescence or young adulthood, affecting primarily peripheral nerves (cranial nerve involvement is rare). Pseudo-onion bulb formation with cylindrical enlargement of the nerve > 2-10 cm. Mitotic activity is rare, MIB-1 labeling index is low. Chromosome 22 loss is characteristic[219], no NF1 association. Treatment: conservative sampling of lesion, not resection
2. soft tissue perineurioma: uncommon. Only rarely can an associated nerve be identified. Almost exclusively benign, but malignant variety does occur. Female:male ratio = 4:1. In males, hands are often affected. Discrete, but not encapsulated, diameter = 1.5-20 cm. Treatment: gross total excision is curative

21.2.25. Miscellaneous primary brain tumors

PRIMARY CNS MELANOMA

Probably arises from melanocytes in the leptomeninges. May spread through CSF pathways. May occasionally metastasize outside the CNS to produce systemic metastases[599].

The peak age for this tumor is in the 4th decade (compared to the 7th decade for primary cutaneous melanoma)[600].

21.3. Pediatric brain tumors

Among all childhood cancers, brain tumors are the second only to leukemias in incidence (20%), and are the most common *solid* pediatric tumor[534], comprising 40-50% of all tumors[138]. Annual incidence: 2-5 cases per 100,000.

Types of tumors

The common pediatric brain tumors are gliomas (cerebellum, brain stem, and optic nerve), pineal tumors, craniopharyngiomas, teratomas, granulomas, and primitive neuroectodermal tumors (**PNETs**, primarily medulloblastoma).

Meningiomas: 1.5% of meningiomas occur in childhood and adolescence (usually between 10-20 years), comprising 0.4-4.6% of intracranial tumors[127 (p 3263)] (see *Meningiomas* on page 613).

Table 21-63 Location of pediatric brain tumors by age

Age	% Infratentorial
0-6 mos	27%
6-12 mos	53%
12-24 mos	74%
2-16 yrs	42%

Infratentorial vs. supratentorial

It has traditionally been taught that most pediatric brain tumors (≈ 60%) are infratentorial, and that these are ≈ equally divided among brain stem gliomas, cerebellar astrocytomas, and medulloblastomas. In reality, the ratio of supratentorial to infratentorial tumors is dependent on the specific age group studied, as illustrated in *Table 21-63*. *Table 21-64* shows the breakdown for pooled data from 1350 pediatric brain tumors.

Astrocytomas are the most common supratentorial tumor in pediatrics as in adulthood.

Table 21-64 Incidence of pediatric brain tumors*

Tumor type	Page	% of total
infratentorial tumors		54%
cerebellar astrocytomas	604	15%
medulloblastomas	686	14%

brain stem gliomas	607	12%
ependymomas[513]	682	9%
supratentorial benign astrocytomas	603	13%

* data from 1350 pediatric brain tumors[126] (p 368)

INTRACRANIAL NEOPLASMS DURING THE FIRST YEAR OF LIFE

Brain tumors presenting during the first year of life is a different subset of tumors than those presenting later in childhood. In a busy neurosurgical unit in a children's hospital, they represented ≈ 8% of children admitted with brain tumors, an average of only ≈ 3 admissions per year[601].

90% of brain tumors in neonates are of neuroectodermal origin, teratoma being the most common. Some of these tumors may be congenital[602]. Other supratentorial tumors include: astrocytoma, choroid plexus tumors, ependymomas, and craniopharyngiomas. Posterior fossa tumors include medulloblastoma and cerebellar astrocytoma.

Many of these tumors escape diagnosis until they are very large in size due to the elasticity of the infant skull, the adaptability of the developing nervous system to compensate for deficits, and the difficulty in examining a patient with limited neurologic repertoire and inability to cooperate. The most common presenting manifestations are vomiting, arrest or regression of psychomotor development, macrocrania, poor feeding/failure to thrive. They may also present with seizures.

21.4. Skull tumors

See *Skull lesions* on page 1219 for differential diagnosis and evaluation (including non-neoplastic lesions). Considering only tumors, the differential diagnosis includes:

1. benign tumors
   A. osteoma: *see below*
   B. hemangioma: *see below*
   C. dermoid and epidermoid tumors: *see below*
   D. chondroma: occur mainly in conjunction with the basal synchondroses
   E. meningioma
   F. aneurysmal bone cyst

2. malignant tumors: malignancy is suggested by a single large or multiple (> 6) small osteolytic lesions with margins that are ragged, undermined and lacking sclerosis[603]
   A. bone metastases to the skull. Common ones include:
      1. prostate
      2. breast
      3. lung
      4. kidney
      5. thyroid
      6. lymphoma
      7. multiple myeloma/plasmacytoma: *see page 740*
   B. chondrosarcoma
   C. osteogenic sarcoma
   D. fibrosarcoma

21.4.1. Osteoma

Osteomas are the most common primary bone tumor of the calvaria. They are benign, slow-growing lesions, that occur commonly in the cranial vault, mastoid and para-nasal air sinuses, and the mandible. Lesions within air sinuses may present as recurrent sinusitis. More common in females, highest incidence is in 6th decade. Triad of Gardner's syndrome: multiple cranial osteomas (of calvaria, sinuses, and mandible), colonic polyposis, and soft-tissue tumors.

See *Localized increased density or hyperostosis of the calvaria* on page 1222 for differential diagnosis.

Pathology

Consists of osteoid tissue within osteoblastic tissue, surrounded by reactive bone. Difficult to distinguish from fibrous dysplasia.

Radiographic evaluation

Skull x-ray: round, sclerotic, well demarcated, homogeneous dense projection. Usually arise from outer table of skull (inner table less common). May be compact or spongy (spongy osteoma may be radiolucent). Unlike meningiomas, diploë are preserved and vascular channels are not increased.

Osteomas are "hot" on nuclear bone scan.

Treatment

Asymptomatic lesions may simply be followed. Surgery may be considered for cosmetic reasons, or if pressure on adjacent tissues produces discomfort. Lesions involving only the outer table may be removed leaving the inner table intact.

21.4.2. Hemangioma

Comprise ≈ 7% of skull tumors[603]. These benign tumors commonly occur in the skull (discussed here) and spine (*see page 738*). Two types: cavernous (most common) and capillary (rare).

Radiographic evaluation

Skull x-ray: characteristically shows a circular lucency with honeycomb or trabecular pattern (seen in ≈ 50% of cases) or radial trabeculations producing a sunburst pattern (seen in ≈ 11% of cases)[603]. Sclerotic margins are evident in only ≈ 33%.

CT: hypodense lesion with sclerotic spaced trabeculations. Nonenhancing.

Bone scan: typically hot.

Treatment

Accessible lesions may be cured by en bloc excision or curettage. The gross appearance is of a hard, blue-domed mass beneath the pericranium. Radiation may be considered for inaccessible tumors.

21.4.3. Epidermoid and dermoid tumors of the skull

See also *page 688* for epidermoids and dermoids in general. Skull involvement is rare and occurs when ectodermal rests are entrapped in the developing skull. Usually midline. Arise within the diploë and expand both inner and outer tables. Identical clinically and radiologically. These benign lesions may involve underlying dural venous structures or brain. They may become infected.

Radiographic evaluation

- **skull x-ray**: these osteolytic lesions have well-defined, sclerotic margins
- some imaging is required to evaluate possible intracranial involvement
  - **CT**: the lesions are hypodense (keratin contains fats), and non-enhancing
  - **MRI**: like CSF they are low intensity on T1WI and high signal on T2WI, but unlike CSF they are high signal on DWI MRI (*see page 690*)

Treatment

Treatment is surgical. Bone margins are curetted. Search must be made for a tract leading to the intracranial cavity which must be followed if found. Preparation for dural sinus repair must be made for lesions overlying the sagittal sinus (including torcular Herophili). Radiation and chemotherapy are not indicated.

21.4.4. Eosinophilic granuloma

A generally benign local disease of bone with mononuclear cells and eosinophils, most commonly found in the skull (43-80%). May also be seen in femur (14.5%), mandible, ribs, pelvis, and the spine (vertebra plana, *see page 729*). Classified as the mildest form of **histiocytosis X** which also includes multifocal eosinophilic granuloma (Hand-Schüller-Christian disease) and Letterer-Siwe syndrome (a fulminant, malignant lymphoma of infancy)[604].

Clinical

Generally a condition of youth, 70% of patients are < 20 yrs age. In a series of 26 patients[604], age range was 18 mos-49 yrs (mean: 16 yrs).

Most common presenting symptom: <u>tender</u>, enlarging skull mass (> 90%). May be asymptomatic and incidentally discovered on skull x-ray obtained for other reasons. Blood tests were normal in all except 1 who had eosinophilia of 23%.

Parietal bone was the most common site (42%), frontal bone next (31%)[604] (some series show frontal bone was the most common).

Evaluation

Skull x-rays

Classic radiographic finding: round or oval non-sclerotic punched out skull lesion with sharply defined margins, involving both inner and outer tables (the disease begins in diploic space), often with beveled edges. A central bone density is occasionally noted (rare, but diagnostic). No abnormal vascularity of adjacent bone. No periosteal reaction. Differentiate from hemangioma by absence of sunburst appearance.

CT scan

Characteristic appearance of a soft tissue mass within area of bony destruction having a central density[605]. Differentiate from epidermoid which has dense surrounding sclerosis.

Pathology

Gross: pinkish gray to purple lesion extending out of bone and involving pericranium. Dural involvement occurs in only 1 of 26 patients, but with no dural penetration.

Microscopic: numerous histiocytes, eosinophils, and multinucleated cells in a reticulin fiber network. No evidence that this is a result of an infection.

Treatment

Tendency toward spontaneous regression, however, most single lesions are treated by curettage. Multiple lesions are usually associated with extracalvarial bony involvement and are often treated with chemotherapy and/or low dose radiation therapy.

Outcome

After a mean 8 years follow-up, 8 patients (31%) developed additional lesions, 5 of these were ≤ 3 yrs age (all of 5 patients < 3 yrs age)[604] (may suggest a form of Letterer-Siwe, thus young patients should be followed closely). Recurrences were local in one case, and in others involved other bones (including the skull, femur, lumbar spine) or brain (including the hypothalamus, presenting with diabetes insipidus and growth delay).

21.4.5. Non-neoplastic skull lesions

Includes:

1. osteopetrosis (*see page 1204*)
2. Paget's disease of the skull (*see page 498*)
3. hyperostosis frontalis interna (*see below*)
4. fibrous dysplasia (*see page 701*)

HYPEROSTOSIS FRONTALIS INTERNA

See page 1222 for differential diagnosis. Hyperostosis frontalis interna **(HFI)** is a benign irregular nodular thickening of the inner table of the frontal bone that is almost always bilateral. The midline is spared at the insertion of the falx. Unilateral cases have been reported[606], and in these cases one must R/O other etiologies such as meningioma, calcified epidural hematoma, osteoma, fibrous dysplasia, an epidural fibrous tumor[607], or Paget's disease.

The incidence of HFI in the general population is ≈ 1.4-5%[606]. HFI is more common in women (female:male ratio may be as high as 9:1) with an incidence of 15-72% in elderly women. A number of possible associated conditions have been described (most are unproven), the majority of which are metabolic, earning it the alias of **metabolic craniopathy**. Associated conditions include:

1. Morgagni's syndrome (AKA Morgagni-Stewart-Morel syndrome): headache, obesity, virilism and neuropsychiatric disorders (including mental retardation)
2. endocrinologic abnormalities
   A. acromegaly[608] (elevated growth hormone levels): *see page 639*
   B. hyperprolactinemia[608]
3. metabolic abnormalities
   A. hyperphosphatemia
   B. obesity
4. diffuse idiopathic skeletal hyperostosis **(DISH)**: *see page 506*

CLINICAL

HFI may present without symptoms as an incidental finding on radiographic evaluation for other reasons. Many signs and symptoms have been attributed to HFI including: hypertension, seizures, headache, cranial nerve deficits, dementia, irritability, depression, hysteria, fatigability and mental dullness. The incidence of headache may be statistically higher in patients with HFI than in the general population[609].

Evaluation

Blood tests to R/O some of the above noted conditions may be indicated in appropriate cases: check growth hormone, prolactin, phosphate, alkaline phosphatase (to R/O Paget's disease).

Plain skull x-ray shows thickening of the frontal bone with characteristic sparing of the midline. Spread to parietal and occipital bone occasionally occurs.

CT demonstrates the lesion which usually causes 5-10 mm of bone thickening, but as much as 4 cm has been reported.

Bone scan: usually shows moderate uptake in HFI (generally not as intense as with bone mets). Also, indium-111 leukocyte scan (commonly used to detect occult infection) will show accumulation in HFI (a false positive)[610, 611].

Treatment

Little has been written about treatment of cases where symptoms are suspected to be due to HFI. In one report, removal of the thickened bone was accomplished without evidence of dural adhesions, and with improvement in the presenting hysteria[606].

Surgical technique

One technique described consists of using the craniotome to excise the thickened portion of the bone (a plain skull x-ray may be used to make a template), and then the thickened bone is thinned down with a high-speed drill, and the bone flap is then replaced. Alternatively, a cranioplasty with methylmethacrylate may be performed.

FIBROUS DYSPLASIA

Usually a benign condition in which normal bone is replaced by fibrous connective tissue (malignant transformation occurs in < 1%). Does not appear to be heritable. Most lesions occur in the ribs or craniofacial bones, especially the maxilla.

Patterns:

1. monostotic: most common
2. polyostotic: 25% with this form have > 50% of the skeleton involved with associated fractures and skeletal deformities
3. as part of McCune-Albright syndrome (endocrine dysfunction, café au lait spots which tend to occur on one side of the midline and tend to be more jagged than those seen in neurofibromatosis (*see page 723*), fibrous

dysplasia, and precocious puberty primarily in females) and its variants

Clinical

Clinical manifestations of the fibrous dysplasia **(FD)** lesions include:

1. incidental finding (i.e. asymptomatic)
2. local pain
3. local swelling (rarely marked distortion resembling aneurysmal bone cyst may occur) or deformity
4. may predispose to pathologic fractures when they occur in long bones
5. cranial nerve involvement: including loss of hearing when the temporal bone is involved as a result of obliteration of the external auditory canal
6. seizures
7. serum alkaline phosphatase is elevated in about 33%, calcium levels are normal
8. darkened hair pigmentation overlying skull lesions
9. spontaneous scalp hemorrhages
10. rarely associated with Cushing's syndrome, acromegaly

3 forms of the FD lesions:

1. cystic (the lesions are not actually cysts in the strict sense): widening of the diploë usually with thinning of the outer table and little involvement of the inner table. Typically occurs high in calvaria
2. sclerotic: usually involves skull base (especially sphenoid bone) and facial bones
3. mixed: appearance is similar to cystic type with patches of increased density within the lucent lesions

Ground glass appearance on x-rays is due to the thin spicules of woven bone.

Treatment

There is no cure for FD. Local procedures (mostly orthopedic) are used for deformities or bone pain that is refractory to other treatment. Neurosurgical involvement may be required for skull lesions producing refractory pain or neurologic symptoms. Calvarial lesions may be treated with curettage and cranioplasty. Calcitonin may be used for wide-spread lesions with bone pain and/or high serum alkaline phosphatase levels.

21.5. Cerebral metastases

Key concepts:

- brain metastases are the most common brain tumor seen clinically
- at the time of onset of neurologic symptoms, 70% will be multiple on MRI
- with solitary brain lesions in a patient with a history of cancer, biopsy should almost always be done since 11% of these lesions will not be mets
- although median survival with maximal treatment is only 8 months (similar to GBM), long-term survivors do occur

METASTASES TO THE BRAIN

Cerebral metastases are the most common brain tumor seen clinically, comprising slightly more than half of brain tumors (if one considers only imaging studies, they comprise ≈ 30%). In the U.S., the annual incidence of new cases of metastases is up to 170,000612, compared to 17,000 for primary brain tumors. 15-30% of patients with cancer **(Ca)** develop cerebral mets[613]. In patients with no Ca history, a cerebral met was the presenting symptom in 15%; of these, 43-60% will have an abnormal chest x-ray **(CXR)**[614, 615] (showing either a bronchogenic primary or other mets to lung).

In 9% of cases, a cerebral met is the only detectable site of spread. Cerebral mets occur in only 6% of pediatric cancers.

The route of metastatic spread to the brain is usually hematogenous, although local extension can also occur.

Solitary mets:

1. CT: at the time of neurologic diagnosis, 50% are solitary on CT[616, 617] (*see page 706*)
2. MRI: if the same patients have an MRI, < 30% will be solitary[618]
3. on autopsy: mets are solitary in one third of patients with brain mets, and 1-3% of solitary mets occur in the brain stem[619]

Increasing incidence of cerebral mets: May be due to a number of factors:

1. increasing length of survival of cancer patients[620] as a result of improvements in treatment of systemic cancer
2. enhanced ability to diagnose CNS tumors due to availability of CT and/or MRI

3. many chemotherapeutic agents used systemically do not cross the blood-brain barrier **(BBB)** well, providing a "haven" for tumor growth there
4. some chemotherapeutic agents may transiently weaken the BBB and allow CNS seeding with tumor

METASTASES OF PRIMARY CNS TUMORS

Spread via CSF pathways

CNS tumors that more commonly spread via CSF pathways include the following (when these tumors spread to the spinal cord, they are often called "drop mets"):

1. high grade gliomas (10-25%) (*see page 597*)
2. primitive neuroectodermal tumors **(PNET)**, especially medulloblastoma (*see page 686*)
3. ependymoma (11%) (*see page 682*)
4. choroid plexus tumors (*see page 695*)
5. pineal region tumors
   A. germ cell tumors (*see page 692*)
   B. pineocytoma and pineoblastoma (*see page 692*)
6. rarely:
   A. oligodendrogliomas (≈ 1%) (*see page 609*)
   B. hemangioblastomas (*see page 671*)
   C. primary CNS melanoma (*see page 697*)

Extraneural spread

Although most CNS tumors do not spread systemically, there is some potential for extraneural spread with the following tumors:

1. medulloblastoma (cerebellar-PNET): the most common primary responsible for extraneural spread. May spread to lung, bone marrow, lymph nodes, abdomen
2. meningioma: rarely goes to heart or lungs
3. malignant astrocytomas rarely metastasize systemically
4. ependymomas
5. pineoblastomas
6. meningeal sarcomas

7. choroid plexus tumors
8. tumors that spread through CSF pathways (*see above*) may spread via a CSF shunt (e.g. to peritoneum with VP shunt or hematogenously with a VA shunt), however, this risk is probably quite small[25]

PRIMARY CANCERS IN PATIENTS WITH CEREBRAL METASTASES

In over 2,700 adults with a primary cancer undergoing autopsy at Sloan-Kettering, the sources of cerebral metastases are shown in *Table 21-65*. Sources of brain metastases in pediatrics is shown in *Table 21-66*.

In adults, lung and breast Ca together account for > 50% of cerebral mets.

In patients with a metastatic brain tumor as the initial presentation (i.e. undiagnosed primary) compared to patients with a known primary, there is about the same number of brain lesions, but there was an increased frequency of extracranial mets 622. In up to 26% of cases, the primary tumor was never identified[622].

Table 21-65 Sources of cerebral mets in adults (autopsy data)

Primary	%
lung Ca	44%
breast	10%
kidney (renal cell)*	7%
GI	6%
melanoma†	3%
undetermined	10%

* a rare tumor that metastasizes frequently to brain (in 20-25% of cases)

† 16% in older series[621]

LOCATION OF CEREBRAL METS

Intracranial metastases may be either parenchymal (≈ 75%) or may involve the leptomeninges in a carcinomatous meningitis (*see page 711*). 80% of solitary metastases are located in the cerebral hemispheres.

The highest incidence of parenchymal mets is posterior to the Sylvian fissure near the junction of temporal, parietal, and occipital lobes (presumably due to embolic spread to terminal MCA branches)[623]. Many tend to arise at the gray/white-matter interface.

The cerebellum is a common site of intracranial mets, and is the location in

16% of cases of solitary brain mets. It is the most common p-fossa tumor in adults, thus “a solitary lesion in the posterior fossa of an adult is considered a metastasis until proven otherwise”. Spread to the posterior fossa may be via the spinal epidural venous plexus (Batson’s plexus) and the vertebral veins.

Table 21-66 Sources of cerebral mets in peds

neuroblastoma
rhabdomyosarcoma
Wilm’s tumor

SPECIFIC TYPES OF CEREBRAL METS

The autopsy incidence of cerebral mets for various types of primary cancers at Sloan-Kettering Cancer Center is shown in *Table 21-67*.

LUNG CANCER

The lungs are the most common source of cerebral mets, and these are usually multiple. The lung primary may be so small as to render it occult.

Necropsy demonstrates cerebral mets in up to 50% of patients with small-cell lung Ca **(SCLC)** and non-squamous, non-small-cell lung Ca[624].

Small-cell lung cancer (SCLC)

AKA “oat cell” Ca. A neuroendocrine tumor. 95% arise in proximal airways, usually in mainstem or lobar bronchi. Typically younger (27-66 years) than other lung Ca. Strongly associated with cigarette smoking. Median survival: 6-10 months. Staged in 1 of 2 categories:

- **limited**: confined to an area of the chest that can be encompassed by a single radiation port
- **extensive**: metastasis outside the thorax or intrathoracic disease that cannot be contained in a single radiation port

Although SCLC comprises only ≈ 20% of primary lung cancers, it is more likely to produce cerebral mets than other bronchogenic cell types (brain mets are found in 80% of patients who survive 2 yrs after diagnosis of SCLC)[620].

Table 21-67 Autopsy incidence of cerebral mets for given primary cancers

Primary	% with cerebral mets
lung	21%

breast	9%
melanoma	40%
lymphoma	1%
Hodgkin's	0
non-Hodgkin's	2%
GI	3%
colon	5%
gastric	0
pancreatic	2%
GU	11%
kidney (renal)	21%
prostate*	0
testes	46%
cervix	5%
ovary	5%
osteosarcoma	10%
neuroblastoma	5%
head and neck	6%

* uncommon, but does occur

Treatment:

Very radiosensitive.

No identified brain mets: prophylactic cranial irradiation **(PCI)** with WBXRT reduces the incidence of symptomatic brain mets and increases survival (disease-free & overall)[625, 626]. Typically 25 Gy in 10 fractions.

Brain mets: surgical resection considered for immediately life-threatening large lesions, XRT is used otherwise. Multiple SCLC brain lesions: XRT (initial treatment 30 Gy in 10 fractions) + chemotherapy.

Treatment of primary: usually not resected. Treated with chemotherapy ± XRT.

Recurrent brain mets after failure of initial treatment: 20 Gy in 10 fractions.

Non-small-cell lung cancer (NSCLC)

Includes: adenocarcinoma (the most common NSCLC), large cell, squamous cell, bronchoalveolar. Retrospective analysis of patients with NSCLC completely resected from lung found a 6.8% first recurrence rate in the brain[624]. Staged with

typical TNM system. Prognosis better than SCLC.

Treatment of lung primary:

1. grades I, II, IIIA (i.e. no distal mets, excluding single brain met): resection
2. higher grades: XRT + chemotherapy

Staging studies for known lung primary

1. PET scan: can detect small malignancies. Useful in NSCLC to determine eligibility of resection of primary. Not useful in initial evaluation of SCLC
2. chest CT: usually includes adrenals and liver (thus abdomen and pelvis CT not necessary)
3. bone scan
4. brain: CT or MRI

When metastatic lung cancer is the suspected source of a newly diagnosed brain lesion, the lung lesion should be biopsied (if technically feasible) to rule out SCLC before obtaining tissue from the cerebral mass.

MELANOMA

Melanoma: the 5th most common cancer in men, 7th in women. Incidence is increasing. Most common sites of origin of melanoma metastases: skin, retina, brain *(primary* CNS melanoma, *see page 697*), nail bed. The primary site cannot be identified in up to ≈ 14% of cases[627]. Extremely difficult to locate primary sites: intraocular, GI mucosa.

Brain mets are found in 10-70% of patients with metastatic melanoma in clinical studies, and in 70-90% on autopsy of patients who died from melanoma. Patients with melanoma who have neurosurgical lesions typically presented 14 months after primary lesion was identified. Once cerebral mets of melanoma are detected, median survival is 113 days, and the mets contributed to the death in 94% of cases[628]. A small group with survival > 3 yrs had a single surgically treated met in the absence of other visceral lesions.

Evaluation

Metastatic melanoma to the brain classically causes pia/arachnoid involvement on imaging. Hemorrhagic involvement is common.

CT: lesions may be slightly hyperdense to brain on unenhanced CT due to melanin. Enhancement is less constant than for other mets (e.g. bronchogenic

Ca).

MRI: decreased signal on T2WI surrounded by intense halo of edema. Enhancing T1WI lesions in a patient with melanoma is highly suggestive of melanoma metastases.

Systemic work-up: systemic disease determines ultimate survival after treatment of melanoma mets to the brain in 70% of patients. ∴ search for systemic mets should be done, including: CT of chest/abdomen/pelvis & bone scan. PET scan may be more sensitive for detecting metastatic spread than CT when there are clinical signs that the tumor has spread[629]; <u>except for the brain</u>, where brain MRI is more sensitive than CT or PET.

Treatment

Surgical indications:

1. patients with CNS metastases that can be completely resected with limited systemic disease: long-term survival is possible
2. patients with intracranial mets that cannot be completely removed or with uncontrolled systemic disease may be surgical candidates for the following:
   A. for symptomatic relief: e.g. lesion causing painful pressure
   B. life-threatening lesion: e.g. large p-fossa lesion with 4th ventricle compression
   C. for hemorrhagic lesion causing symptoms by mass effect from the clot

Whole-brain radiation therapy **(WBXRT)**:

Melanoma is typically radioresistant. WBXRT provides 2-3 month survival benefit and may be considered for palliation in patients with multiple mets that preclude complete excision or SRS.

Stereotactic radiosurgery **(SRS)**:

Considered for ≤ 3 lesions all ≤ 3 cm diameter that are surgically inaccessible, with limited or quiescent systemic involvement. Relative contraindications: hemorrhagic lesions, lesions with significant mass effect surrounding edema.

Chemotherapy:

1. dacarbazine: the gold-standard treatment for melanoma. An alkylating agent which is about equally as effective as its newer <u>orally</u> administered analog temozolomide (Temodar®). Response rate: 10-20%
2. interferon and interleukin: interleukin-2 **(IL-2)** has been associated with

significant cerebral edema in patients with melanoma mets in the brain, therefore therapy is withheld unless all mets can be removed prior to therapy 630

3. bevacizumab (Avastin®): monoclonal antibody to vascular endothelial growth factor (VGEF)
4. BAY 43-9006 (inhibits BRAF kinase - BRAF oncogene mutation is common in melanoma) used in conjunction with carboplatin and paclitaxel with a 50% response in Phase I trials
5. immunotherapy: Melacine® vaccine (melanoma tumor cell lysates + immunologic adjuvant Detox) is as effective as chemotherapy with fewer side effects. Used for treatment of documented melanoma, not as a preventative vaccine

Suggested algorithm for patients with metastatic melanoma to the brain[631]:

1. Karnofsky performance scale **(KPS)** score < 70 (*see page 1182*): chemotherapy
2. KPS ≥ 70
   A. active systemic disease:
      1. life expectancy > 3 months: WBXRT
      2. life expectancy ≤ 3 months: no treatment
   B. no active systemic disease:
      1. surgically accessible lesions: resection + WBXRT
      2. surgically inaccessible lesions
         a. ≤ 3 lesions all ≤ 3 cm diameter: SRS + WBXRT
         b. > 3 lesions or any lesion > 3 cm diameter: WBXRT

Outcome

1. older studies with single CNS met and quiescent systemic disease: 8-10 months median survival
2. more recent study with active systemic disease and multiple intracranial lesions[632]: 18 months median survival, 20% 5-year survival
3. the presence of infratentorial lesions is a poor prognosticator

RENAL-CELL CARCINOMA

AKA hypernephroma. Usually associated with spread to lungs, lymph nodes, liver, bone (high affinity for bone), adrenals, and contralateral kidney before invading the CNS (thus, this tumor rarely presents as isolated cerebral

metastases). Look for hematuria, abdominal pain, and/or abdominal mass on palpation or CT. Response to XRT is only ≈ 10%.

CLINICAL PRESENTATION

As with most brain tumors, signs and symptoms are usually slowly progressive compared to those from vascular events (ischemic or hemorrhagic infarcts) which tend to be sudden in onset and slowly resolve, or electrical events (seizures) which tend to be sudden in onset and rapidly resolve. There are no findings that would allow differentiation of a metastatic tumor from a primary neoplasm on clinical grounds.

Signs and symptoms include:

1. those due to increased ICP from mass effect and/or blockage of CSF drainage (hydrocephalus):
   A. headache **(H/A)**: the most common presenting symptom, occurs in ≈ 50%
   B. nausea/vomiting
2. focal deficits:
   A. due to compression of brain parenchyma by mass and/or peritumoral edema (e.g. monoparesis without sensory disturbance)
   B. due to compression of cranial nerve
3. seizures: occur only in ≈ 15% of cases
4. mental status changes: depression, lethargy, apathy, confusion
5. symptoms suggestive of a TIA (dubbed “tumor TIA”) or stroke, may be due to:
   A. occlusion of a vessel by tumor cells
   B. hemorrhage into the tumor, especially common with metastatic melanoma, choriocarcinoma, and renal-cell carcinoma[633] (see *Hemorrhagic brain tumors*, page 1123). May also occur due to decreased platelet count

EVALUATION

IMAGING STUDIES (CT OR MRI)

Metastases usually appear as “non-complicated” masses on CT (i.e. round, well circumscribed), often arising at the gray/white junction. Characteristically, profound white matter edema (“fingers of edema”) reach deep into brain from

the tumor, usually more pronounced than that seen with primary (infiltrating) brain tumors. When multiple lesions are present (on CT or MRI of brains with multiple mets) Chamber's rule applies: "Whoever counts the most mets is right." Mets usually enhance, and must be considered in the differential diagnosis of a ring-enhancing lesion.

Solitary supratentorial lesion on CT[614]

• brain mets from solid tumors are solitary on CT in 50-65% of cases
• with negative Ca history, negative CXR and negative IVP (presumably, this would also apply if a chest/abdominal/pelvic CT was negative): 7% of solitary lesions are mets, 87% are primary brain tumors, and 6% are nonneoplastic. Yield of further work-up to find primary is low (recommendation: follow serial CXRs)
• with history of treated Ca: 93% of solitary lesions are mets

MRI

More sensitive than CT, especially in the p-fossa (including brain stem). Detects multiple mets in ≈ 20% of single mets on CT[613]. Multiple projections may also assist in surgical planning.

LUMBAR PUNCTURE

Relatively contraindicated when there is a cerebral mass (may be indicated once mass lesion has been ruled out). May be most useful in diagnosing carcinomatous meningitis (*see Carcinomatous meningitis*, page 711).

METASTATIC WORK-UP

Prior to obtaining tissue from brain lesion: When metastatic disease is suspected based on imaging or on surgical tissue, a search for a primary site and assessment for other lesions may be considered since it may provide alternative sites for tissue for histologic diagnosis, and it may guide treatment (e.g. widely disseminated metastases may preclude aggressive therapy). Metastatic work-up should include:

1. CXR: to rule out lung primary or other mets to lung
2. CT of the chest (more sensitive that CXR), abdomen and pelvis: to rule out renal or GI primary (second choice: IVP) or liver mets
3. test stool for occult blood

4. radionuclide bone scan: for patients with bone pain or for tumors that tend to produce osseous metastases (especially: prostate, breast, kidney, thyroid & lung)
5. mammogram in women
6. prostate specific antigen (PSA) in men
7. PET scan: can detect small malignancies

Cancer of unknown primary site (CUP): If the metastatic work-up (*see above*) is negative, the pathology of a metastatic brain lesion may implicate specific primary sites.

Small-cell carcinoma metastatic to the brain is most likely from the lung. Stains positive for **neuroendocrine** stains (*see page 721*).

Adenocarcinoma: lung is the most common primary. Other sources: GI (mostly colon), breast. The primary site may remain occult even after extensive evaluation in up to 88%[634]. Immunostaining has been tried to identify the primary site but has not been found to be widely useful.

MANAGEMENT

With optimal treatment, median survival of patients with cerebral mets is still only ≈ 26-32 weeks, therefore management is mostly palliative (also see *Outcome*, page 710 for comparison of various treatments).

Confirming the diagnosis

Caution: 11% of patients with abnormalities on brain CT or MRI with a history of cancer (within past 5 yrs) do not have cerebral metastases[635]. Differential diagnoses include: glioblastoma, low grade astrocytoma, abscess, and nonspecific inflammatory reaction. If non-surgical treatment (e.g. chemotherapy or RTX) is being contemplated, the diagnosis should be confirmed by biopsy in almost all cases.

MANAGEMENT DECISIONS

Prognostication

This is critical since many treatment decisions depend on overall prognosis.

RTOG RPA: Radiation Therapy Oncology Group recursive partitioning analysis

classification[636] (*see Table 21-68*) (from 1200 patients with brain metastases undergoing XRT). Conclusion: the specific tumor type, length of time since diagnosis, etc. are not as important prognostically as the Karnofsky Performance Scale **(KPS)** score (*see page 1182*).

RPA Class 3 patients have been shown to be unlikely to benefit from any of numerous treatment modalities studied. Class 1 are more likely to benefit. Most patients are Class 2, and benefit is unclear.

Table 21-68 RPA Classification for patients with brain mets

RPA class	Description	Median survival (mos)*
1	• KPS† $\geq$ 70 and • age < 65 years and • no systemic disease	7
2	• all others‡	4
3	• KPS < 70	2

* for patients undergoing XRT

† KPS = Karnofsky Performance Scale score (see page 1182)

‡ i.e. not RPA class 1 or 3

Management algorithm

Table 21-69 shows a summary of management suggestions (details appear in following sections).

Also, surgical excision may be considered for patients with completely resectable brain mets who are candidates for chemotherapy with interleukin-2 **(IL-2)** for systemic disease (e.g. for renal-cell Ca or melanoma) since this drug in some case reports produces significant cerebral edema if there are cerebral mets as well.

MEDICAL MANAGEMENT

Initial treatment:

1. anticonvulsants: e.g. phenytoin. Generally not needed for posterior fossa lesions
2. corticosteroids: many symptoms are due to peritumoral edema (which is primarily vasogenic), and respond to steroids within 24-48 hrs. This improvement is not permanent, and prolonged steroid administration may produce side effects (see *Possible deleterious side effects of steroids*, page 33).

Rx typical dose for a patient with significant symptoms who is not already on steroids: dexamethasone (Decadron®) 10-20 mg IV, followed by 6 mg IV q 6 hrs for 2-3 days, after which it is converted to ≈ 4 mg PO QID. Once symptoms are controlled, this is tapered to ≈ 2-4 mg PO TID as long as symptoms do not worsen

3. H_2 antagonists (e.g. ranitidine 150 mg PO q 12 hrs)

CHEMOTHERAPY

Limitations of chemotherapy in the brain are discussed on *page 589*. If multiple lesions of known small-cell Ca are detected on cerebral imaging, treatment of choice is radiation plus chemotherapy.

Table 21-69 Management suggestions for cerebral metastases*

Clinical situation		Management
unknown primary or unconfirmed diagnosis		stereotactic biopsy for ≈ all patients if surgical excision is not a consideration
uncontrolled widespread systemic cancer & obviously short life expectancy and/or poor performance status (Karnofsky ≤ 70, *see page 1182*)		(biopsy as indicated above) + WBXRT or no treatment
Stable systemic disease & KPS > 70		
solitary met	symptomatic, large, or accessible lesion	surgical excision + WBXRT
	asymptomatic, small, or inaccessible lesion	WBXRT ± SRS boost
multiple mets	single large lesion that is life threatening or producing mass effect	surgery for the large lesion + WBXRT for the rest
	≤ 3 lesions: symptomatic & can all be removed	surgery + WBXRT or SRS + WBXRT
	≤ 3 lesions: cannot all be removed	WBXRT or SRS + WBXRT
	> 3 lesions: with no mass effect requiring surgery	WBXRT[638]

* adapted[637]. Abbreviations: WBXRT = whole brain radiation therapy, SRS = stereotactic radiosurgery

RADIATION THERAPY

Caution: not all brain lesions in cancer patients are mets (*see above*).

In patients not considered for surgery, steroids and radiation usually help H/A, and in ≈ 50% of cases symptoms improve or completely resolve[639]. This does not result in local control for the majority of these patients and they frequently succumb from progressive brain disease.

The usual dose is **30 Gy in 10 fractions given over 2 weeks**. With this dose, 11% of 1-yr survivors and 50% of 2-yr survivors develop severe dementia.

"Radiosensitivity" of various metastatic tumors to whole brain radiation therapy **(WBXRT)** are shown in *Table 21-70*.

Prophylactic cranial irradiation

Prophylactic cranial irradiation after resection of small-cell lung carcinoma **(SCLC)** reduces relapses in brain, but does not affect survival[640].

Table 21-70 "Radiosensitivity" of brain metastases to WBXRT

Radiosensitivity	Tumor
Radiosensitive[635]	• small-cell lung Ca • germ-cell tumors • lymphoma • leukemia • multiple myeloma
Moderately sensitive	• breast
Moderately resistant	• colon • non small-cell lung cancer
Highly resistant*	• thyroid • renal cell (10% respond) • malignant melanoma • sarcoma • adenocarcinoma

* SRS may be better than WBXRT for these

Post-op radiation therapy

WBXRT is usually recommended following craniotomy for metastatic disease[641], especially with SCLC where "micro-metastases" are presumed to be present throughout brain[A].

A. some centers do not routinely administer post-op WBXRT (except for very radiosensitive tumors such as SCLC) but instead follow patients with serial imaging studies and administer XRT only when metastases are documented

Optimal dose is controversial. Early reports recommended 30-39 Gy over 2-2.5 weeks (3 Gy fractions) with or without surgery[642]. This is acceptable in patients not expected to live long enough to get long-term radiation effects.

Recent recommendations are for smaller daily fractions of 1.8-2.0 Gy to reduce neurotoxicity[643]. These low doses are also associated with a higher rate of recurrent brain metastases[644]. Since 50 Gy are needed to achieve > 90% control of micrometastases, some use **45-50 Gy WBXRT**, plus a boost to the tumor bed to bring the total treatment up to 55 Gy, all with low **fractions of 1.80-2.0 Gy**[645].

Stereotactic radiosurgery

Inconsistent in its ability to reduce tumor size. Some retrospective studies show results comparable to surgery[646]. Other do not[647]. Does not obtain tissue for histological analysis, and cannot be used for lesions > 3 cm. Also, *see page 710*.

SURGICAL MANAGEMENT

SOLITARY LESIONS

Indications favoring surgical excision of a solitary lesion:

1. primary disease quiescent
2. lesion accessible
3. lesion is symptomatic or life-threatening
4. primary tumor known to be relatively radioresistant (excision is rarely indicated for untreated brain metastases from SCLC because of its radiosensitivity)
5. for recurrent SCLC following XRT
6. diagnosis unknown: alternatively consider biopsy, e.g. stereotactic biopsy

Surgical resection in patients with progressive systemic disease and/or significant neurologic deficit is probably unjustified[648]. Also, in newly diagnosed cancer patients, craniotomy may delay systemic treatment for weeks and the ramifications of this need to be considered.

MULTIPLE LESIONS

Patients with multiple metastases generally have much worse survival than those with solitary lesions[643]. Multiple metastases are usually treated with XRT without surgery. However, if total excision of all mets is feasible, then even multiple mets may be removed with survival similar to those having a single met removed[649] (also *see Table 21-69* for summary). If only incomplete excision is possible (i.e. cannot remove all mets, or portions of 1 or more must be left

behind) then there is no improvement in survival with surgery, and XRT alone is recommended. The mortality of removing > 1 met at a single sitting is not statistically significantly higher than removing a single met.

Situations where surgery may be indicated for multiple mets[650]:

1. one particular and accessible lesion is clearly symptomatic and/or life threatening (life-threatening lesions include p-fossa and large temporal lobe lesions). This is palliative treatment to reduce the symptom/threat from that particular lesion
2. multiple lesions that can all be completely removed (*see above*)
3. no diagnosis (e.g. no identifiable primary): consider stereotactic biopsy

Stereotactic biopsy

Considered for:

1. lesions not appropriate for surgery. Includes cases with no definite diagnosis and:
   A. deep lesions
   B. multiple small lesions
2. patients not candidates for surgical resection
   A. poor medical condition
   B. poor neurologic condition
   C. active or widespread systemic disease
3. to ascertain a diagnosis
   A. when another diagnosis is possible: e.g. no other sites of metastases, long interval between primary cancer and detection of brain mets…
   B. especially if nonsurgical treatment modalities are planned (*see above*)

Intra-operative considerations for surgical removal

Most lesions present themselves on the surface of the brain or through the dura. For lesions not visible on the surface nor palpable immediately beneath the surface, intraoperative ultrasound or stereotactic techniques may be used to localize the lesion.

Metastases usually have a well defined border, thus a plane of separation from normal brain may be exploited, often allowing gross total removal.

Outcome

Table 21-71 lists factors associated with better survival regardless of

treatment. Also, the prognosis gets worse as the number of mets increases[637]. Median survival even with best treatment in some studies is only ≈ 6 months.

Natural history

By the time that neurologic findings develop, median survival among untreated patients is ≈ 1 month[651].

Steroids

Using steroids alone (to control edema) doubles survival[652] to 2 mos[A].

A. NB: this is based largely on pre-CT era data, and the tumors were therefore probably larger than in current studies[653]

Table 21-71 Factors associated with better prognosis for brain mets (with any treatment)

• Karnofsky score* (KPS) > 70
• age < 60 yrs
• metastases to brain only (no systemic mets)
• absent or controlled primary disease
• > 1 yr since diagnosis of primary
• the fewer the number of brain mets
• female gender

* the KPS (see page 1182) is probably the most important predictor; those with a score of 100 had median survival > 150 weeks

Whole brain radiation therapy (WBXRT)

WBXRT + steroids increases survival to 3-6 mos[649]. 50% of deaths are due to progression of intracranial disease.

Surgery ± WBXRT

Recurrence of tumor was significantly less frequent and more delayed with the use of post-op WBXRT[641]. Length of survival was unchanged with supplemental use of WBXRT. There is also an additional loss of cognitive function in many cases, and patients are rarely independent after WBXRT.

In 33 patients treated with surgical resection of single mets and post-op WBXRT[654]: median survival was 8 months; with 44% 1-yr survival. If no evidence of systemic Ca, 1-yr survival is 81%. If systemic Ca is present (active or inactive), 1-yr survival is 20%. Patients with solitary mets and no evidence of active systemic tumor have the best prognosis[639, 648]. With total removal, no recurrence nor new parenchymal mets occurred within 6 months, and the major cause of death was progression of Ca outside the CNS. A randomized trial verified the improved longevity and quality of survival of patients with solitary mets undergoing surgical excision plus WBXRT vs. WBXRT alone (40 weeks vs. 15 weeks median survival)[635]. The surgical mortality was 4% (≈ same as 30-day mortality in the RTX-only group). More patients treated with WBXRT alone die of their brain mets than those who underwent surgery. Following total removal and post-op WBXRT, 22% of patients will have recurrent brain tumor at 1 year[643]. This is better than surgery without XRT (with reported failure rates of 46%[643] and 85%[644]).

Stereotactic radiosurgery (SRS)

Also, *see page 778*. There has not been a randomized study to compare surgery to SRS. Retrospective studies *suggest* that SRS may be comparable to surgery[646, 655]. How-ever, a prospective (non-randomized, retrospectively matched) study[647] found a median survival of 7.5 mos with SRS vs. 16.4 mos with surgery, and a higher mortality from cerebral disease in the SRS group (with the mortality due to the SRS treated lesions and not new lesions). A local control rate of ≈ 88% has been reported, with one study also recommending WBXRT following the SRS for better regional control[656].

Actuarial control rates at 1 year following SRS + WBXRT were 75-80% and appear to be similar to surgery + WBXRT[637]. However, SRS was unreliable in reducing tumor size.

Multiple mets

Patients with multiple mets that were totally removed have a survival that is similar to those having single mets surgically removed[649] (*see above*).

21.6. Carcinomatous meningitis

Carcinomatous meningitis **(CM)** AKA (lepto) **meningeal carcinomatosis (LMC)**. Found in up to 8% of patients autopsied with systemic Ca. Up to 48% may present with CM before the presence of systemic Ca is known. Most common primaries: breast, lung, then melanoma[267 (p 610-2)]. Always include lymphomatous meningitis in the differential diagnosis (see *CNS lymphoma*, page 672).

CLINICAL

Simultaneous onset of findings in multiple levels of neuraxis. Multiple cranial nerve findings are frequent (in up to 94%, most common: VII, III, V & VI), usually progressive. Most frequent symptoms: H/A, mental status changes, lethargy, seizure, ataxia. Non-obstructive hydrocephalus is also common. Painful radiculopathies can occur with “drop mets”.

DIAGNOSIS

Lumbar puncture

Perform only after mass lesion has been ruled out with cranial CT or MRI. Although the initial LP may be normal, CSF is eventually abnormal in > 95%.

CSF should be sent for:

1. cytology to look for malignant cells (requires ≈ **10 ml** for adequate evaluation for CM). Repeat if negative (45% positive on first study, 81% eventually positive after up to 6 LPs). May need to pass CSF through a millipore filter
2. bacterial and fungal cultures (including unusual organisms, e.g. cryptococcus)
3. tumor markers: carcinoembryonic antigen, alpha-fetoprotein
4. protein/glucose: elevated protein is the most common abnormality. Glucose may be as low as ≈ 40 mg% in about a third of patients

MRI

Contrast enhanced MRI is more sensitive in showing meningeal enhancement[657].

CT

May show (mild) ventricular dilatation, enhancement of basal cisterns. Sulcal enhancement may also occur with involvement of the convexities.

Myelography

Spinal seeding ("drop mets") will produce filling defects on myelography.

SURVIVAL

Untreated: < 2 months. With radiation therapy + chemotherapy: median survival is 5.8 mos (range 1-29). Chemotherapy may be given intrathecally. About half of patients die of CNS involvement, and half die of systemic disease.

21.7. Foramen magnum tumors

DIFFERENTIAL DIAGNOSIS

See *Foramen magnum lesions* on page 1212 for nonneoplastic lesions. Most foramen magnum **(FM)** region tumors are extra-axial. This includes:

1. meningioma: the anterior lip of the foramen magnum is the second most common site of origin of posterior fossa meningiomas. Meningiomas comprise 38-46% of FM tumors[192, 193] (*see page 614*) and most are intradural
2. chordoma
3. neurilemmoma
4. epidermoid
5. chondroma
6. chondrosarcoma
7. metastases
8. exophytic component of a brainstem tumor

PRESENTATION

In the pre-imaging era (i.e. before CT & MRI) these lesions were often diagnosed relatively late due to the unusual associated clinical syndromes and the rarity of visualizing this region on myelography.

CLINICAL FINDINGS

Symptoms:

1. sensory
   A. craniocervical pain: usually an early symptom, commonly in neck and occiput. Aching in nature. ↑ with head movement
   B. sensory findings: usually occur later. Numbness and tingling of the fingers
2. motor
   A. spastic weakness of the extremities: weakness usually starts in the ipsilateral UE, then the ipsilateral LE, then contralateral LE, and finally contralateral UE ("rotating paralysis")

Signs:

1. sensory
   A. dissociated sensory loss: loss of pain and temperature contralateral to lesion with preservation of tactile sensation
   B. loss of position and vibratory sense, greater in the upper than the lower extremities
2. motor
   A. spastic weakness of the extremities
   B. atrophy of the intrinsic hand muscles: a lower motor nerve finding
   C. cerebellar findings may rarely be present with extensive intracranial extension
3. long tract findings
   A. brisk muscle stretch reflexes (hyperreflexia, spasticity)
   B. loss of abdominal cutaneous reflexes
   C. neurogenic bladder: usually a very late finding
4. ipsilateral Horner's syndrome: due to compression of cervical sympathetics
5. nystagmus: classically downbeat (*see page 828*), but other types can occur

It had been postulated that long tract findings were due to direct compression at the cervicomedullary junction, and that lower motor nerve findings in the upper extremities were due to central necrosis of the grey matter as a result of compression of arterial blood supply. Anatomic study suggests that it is actually venous infarction at lower cervical levels (C8-T1) that is responsible for the lower motor neuron findings.

SURGICAL TREATMENT

Surgical approaches:

1. transoral approach: *see* *page 176* for technique
   A. disadvantage: cannot reach to > 1 cm to either side of midline
   B. almost exclusively for extradural lesions (although some intra-axial lesions have been approached, the experience is extremely limited)
2. extreme lateral transcondylar approach
   A. disadvantage: lack of familiarity of most neurosurgeons with this approach
   B. advantage: excellent exposure of anterior foramen magnum with proximal control of vertebral artery
3. lateral posterior fossa approach: see *Posterior fossa (suboccipital) craniectomy*, page 152 for technique
   A. disadvantage: cannot reach midline or contralateral component, however, some tumor in these regions may be pulled into the field as the tumor is debulked

21.8. Idiopathic intracranial hypertension (IIH)

Key concepts:

- papilledema and symptomatic ICP elevation > 25 cm H_2O in the absence of intracranial mass or infection. Often associated with dural sinus thrombosis
- a preventable cause of (often permanent) blindness from optic atrophy
- more common in obese females of childbearing age than general population
- recommended work-up:
  - preferred imaging studies: ✔ brain MRI (without & with contrast) and MRV. Imaging should be normal (allowed exception: slit-like ventricles)
  - ✔ LP. Findings: opening pressure (> 20 cm H_2O) & normal CSF analysis
  - ✔ ophthalmologic eval: test visual fields, acuity, and check for papilledema
- usually self-limited, recurrence is common, chronic in some patients
- risk of blindness is not reliably correlated to duration of symptoms, papilledema, H/A, Snellen visual acuity, or number of recurrences
- treatment for patients failing medical management (weight loss, Diamox…):
  - optic nerve sheath fenestration **(ONSF)** is best for visual loss without H/A
  - CSF shunt may be better than ONSF for H/A associated with visual loss

AKA **pseudotumor cerebri**, AKA **benign intracranial hypertension**, (plus numerous other obsolete terms[658]) is a heterogeneous group of conditions characterized by increased intracranial pressure with no evidence of intracranial mass, hydrocephalus, infection (e.g. chronic fungal meningitis), or hypertensive encephalopathy. Some, but not all, authors exclude patients with intracranial hypertension in the presence of dural sinus thrombosis. IIH is thus a diagnosis of exclusion. There is a juvenile and an adult form.

EPIDEMIOLOGY

1. female:male ratio reported from 2:1 to 8:1 (no gender difference in juvenile form)
2. obesity is reported in 11-90% of cases, and is not as prevalent in men[659]
3. incidence among obese women of childbearing years[660, 661]: 19-21/100,000, (whereas incidence in general population[658]: 1-2/100,000)
4. peak incidence in 3rd decade (range: 1-55 years). 37% of cases are in children, 90% of these are age 5-15 years. Very rare in infancy
5. frequently self limited (recurrence rate: 9-43%)
6. severe visual deficits develop in 4-12%, unrelated to duration of symptoms, degree of papilledema, headache, visual obscuration, and number of recurrences[662]. Perimetry is the best means to detect and follow visual loss

PATHOGENESIS

Not fully understood. Increased cerebral edema & brain water content, increased venous pressure & cerebral blood volume, and reduced CSF absorption have all been demonstrated. Theories that also explain the high prevalence in obese females:

1. mechanical theory: obesity → ↑ intraabdominal pressure → ↑ central venous pressure → ↓ CSF resorption → ↑ ICP[A]
2. hormonal theory: adipocytes convert androstenedione → estrone → ↑ CSF production

A. however, other studies have indicated that elevated venous pressure may actually be an epiphenomenon to a primary increase in ICP[663]

Table 21-72 Modified Dandy's criteria for IIH

- signs & symptoms of increased ICP
- no localizing signs other than Cr. N VI palsy* in an otherwise awake and alert patient
- increased CSF pressure without chemical or cytological abnormalities
- normal to small ventricles and no intracranial mass

* may result from ↑ ICP (*see page 836*)

DIAGNOSTIC CRITERIA

Modified Dandy's criteria are shown in *Table 21-72*.

More specifically, four diagnostic criteria[664]:

1. CSF pressure: > 25 cm H_2O (pressures > 40 are not uncommon)[A]. Pressures 20-24.9 are nondiagnostic[665]. Pressure < 20 is normal
2. CSF composition: normal glucose and cell count. Protein is normal, or in ≈ two thirds of cases it is low (< 20 mg%)
3. symptoms & signs are those of elevated ICP alone (i.e. papilledema & H/A) with no focal findings (allowed exception: abducens nerve palsy which may be due to increased ICP, *see page 836*)
4. normal radiologic studies of the brain (CT or MRI) with the allowed exceptions of:
   A. the occasionally seen slit ventricles (the incidence may be no higher in IIH than in age-matched controls[666]) or empty sella
   B. infantile form may have generous ventricles and large fluid spaces over brain
   C. intra-orbital abnormalities may be seen: *see below*

CLINICAL

PRESENTATION[664, 667]

- symptoms
  A. classic (major) symptoms
     1. H/A (the most common symptom): 94-99%. Typically retro-ocular and pulsatile. May ↑ with eye movement. Severity does not correlate with degree of CSF pressure elevation. Occasionally worse in A.M.
     2. nausea: 32% (actual vomiting is less common)
     3. visual loss (see *Visual loss in IIH* below):
        a. transient visual obscuration **(TVO)**

b. permanent afferent visual pathway injury
4. diplopia (more common in adult, usually due to VI nerve palsy): 30%

B. minor symptoms[668]
1. neck stiffness: 30-50%
2. tinnitus[B]: up to 60%. Usually pulse synchronous. Described as rushing noise. May be unilateral (in these, may be reduced by ipsilateral jugular vein compression + ipsilateral head rotation)
3. ataxia: 4-11%
4. acral paresthesias: 25%
5. retrobulbar eye pain on eye movements
6. arthralgia[B]: 11-18%
7. dizziness: 32%
8. fatigue
9. reduced olfactory acuity

• signs (generally restricted to visual system)

A. eye findings - also see *Visual loss in IIH* below
1. papilledema:
   a. present in almost ≈ 100%
   b. idiopathic intracranial hypertension without papilledema **(IIHWOP)**[669]: a variant of IIH. Visual loss tends not to occur
   c. usually bilateral, occasionally unilateral[670]
   d. may be mild (subtle nerve fiber elevation)
2. abducens nerve (Cr. N. VI) palsy: 20% (a false localizing sign, *see page 836*). The esotropia ranges from < 5 prism diopters dysconjugate angle in primary gaze to > 50671
3. visual acuity: relatively insensitive assessment of visual function
4. visual field defect: 9%.
   a. early changes: peripheral fields & nasal quadrant defect
   b. enlarged blind spot (66%) and concentric constriction of peripheral fields (blindness is very rare at presentation)

B. infantile form may have only enlarging OFC, frequently self limited, usually requires only follow-up without specific treatment

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A. diurnal variations in CSF pressure may occasionally cause a falsely low (i.e normal) reading. ∴ if clinical suspicion is high, an LP at a different time of day or continuous ICP monitoring may be required
B. the causal relationship with IIH has been demonstrated by resolution of these symptoms with reduction of CSF pressure

C. conspicuous absence of altered level of consciousness in spite of high ICP

Worsening of any of the above symptoms with postural changes that increase ICP (bending over, Valsalva maneuver…) is characteristic in idiopathic intracranial hypertension.

Visual loss in IIH

Quoted range of occurrence in IIH: 48-68% (lower numbers generally come from population based samples). A prospective study found changes by Goldman perimetry in 96% of 50 patients[672]. The only parameter associated with worsening vision is recent weight gain.

Pathomechanics: Increased ICP is transmitted along optic nerve sheath → circumferential compression of the retinal ganglion cell axons at the level of the lamina cribrosa[671].

Manifestations:

1. transient **visual obscurations (TVO)**: graying or blacking out of vision. Lasts ≈ 1 second. Uni- or bilateral. Typically occur with eye movement, bending over or valsalva maneuver. Directly proportional to severity of papilledema. Frequency of TVOs parallels ICP elevation, but doesn't correlate with permanent visual loss
2. visual loss in IIH may occur early or late, may be sudden or gradually progressive, and is not reliably correlated to duration of symptoms, papilledema, H/A, Snellen visual acuity, or number of recurrences. It may escape detection until profound.
   A. early: usually constriction of fields and loss of color (∴ perimetry is the best test for following vision in IIH)
   B. late: central vision is affected. Findings include: concentric constrictions, enlargement of the blind spot, inferior nasal defects, arcuate defects, cecocentral scotomas…

Table 21-73 Conditions that may be associated with IIH[673]

Proven association
Meets 4 criteria from *Table 21-74*
• obesity
Likely association

Meets 3 criteria from *Table 21-74*
• drugs: keprone, lindane • hypervitaminosis A
Probable association
Meets 2 criteria from *Table 21-74*
• steroid withdrawal* • thyroid replacement in children • ketoprofen & indomethacin in Bartter syndrome • hypoparathyroidism • Addison's disease* • uremia • iron deficiency anemia • drugs: tetracycline, nalidixic acid, Danazol, lithium, amiodarone, phenytoin, nitrofurantoin, ciprofloxacin, nitroglycerin
Possible association
Meets 1 criterion from *Table 21-74*
• menstrual irregularity • oral contraceptive use† • Cushing's syndrome • Vitamin A deficiency • minor head trauma • Behçet syndrome
Unlikely association
Meets none of the criteria in *Table 21-74*
• hyperthyroidism • steroid use • immunization
Unsupported association
• pregnancy • menarche

* may respond to steroids

† may be associated with dural sinus thrombosis, see text

Associated conditions

By definition, IIH is idiopathic. However, often what is considered "IIH" may actually be secondary to some other condition (e.g. transverse sinus thrombosis, *see below*). Many conditions cited as associations with IIH may be coincidental. Four criteria suggested to establish a cause-effect relationship are shown in *Table 21-74*[667].

Table 21-74 Criteria for causality of IIH by another condition[667]

1. meets Dandy's criteria (*Table 21-72*, page 713) 2. the condition should be proven to increase ICP

3. treatment of the condition should improve the IIH	
4. properly controlled studies should show an association between the condition and IIH	

Table 21-73 shows a scale[673] to rank the likelihood of association between various conditions and IIH based on the number of the criteria met in *Table 21-74*.

Other conditions not included in this list that meet minimal criteria but are unconfirmed in case-control studies[658] include:

1. other drugs: isotretinoin (Accutane®), trimethoprim-sulfamethoxazole, cimetidine, tamoxifen
2. systemic lupus erythematosus **(SLE)**

Conditions that may be related by virtue of increased pressure in the dural sinuses (*see below*) (some have called this "secondary IIH" which is an oxymoron):

1. otitis media with petrosal extension (so-called otitic hydrocephalus)
2. radical neck surgery with resection of the jugular vein
3. hypercoagulable states

Venous hypertension & sinovenous abnormalities

Venous hypertension has often been proposed as a unifying underlying cause of IIH. Abnormalities of the dural sinuses, including thrombosis, stenosis[674], obstruction, or elevated pressure have been demonstrated. While these findings may underlie a significant number of cases, they may in actuality be epiphenomena (e.g. venous hypertension may be due to compression of the transverse sinuses by elevated intracranial pressure[663]), and it is unlikely that such abnormalities will explain all cases.

Differential diagnosis

1. true mass lesions: tumor, cerebral abscess, subdural hematomas, rarely gliomatosis cerebri may be undetectable on CT and will be misdiagnosed as IIH
2. cranial venous outflow impairment (some authors consider these as IIH)[675]
   A. dural sinus thrombosis (*see above* and *page 1166*)
   B. congestive heart failure
   C. superior vena cava syndrome

D. unilateral or bilateral jugular vein or sigmoid sinus[676] obstruction
E. hyperviscosity syndromes
F. Masson's vegetant intravascular hemangioendothelioma[677]: an uncommon, usually benign lesion that may rarely involve the neuraxis (including intracranial occurrence)

3. Chiari I malformation **(CIM)**: may produce findings similar to IIH. 6% of IIH patients have significant tonsillar ectopia, and ≈ 5% of patient with CIM have papilledema[671]
4. infection (CSF will be abnormal in most of these): encephalitis, arachnoiditis, meningitis (especially basal meningitis or granulomatous infections, e.g. syphilitic meningitis, chronic cryptococcal meningitis), chronic brucellosis
5. inflammatory conditions: e.g. neurosarcoidosis (*see page 71*), SLE
6. vasculitis: e.g. Behçet's syndrome
7. metabolic conditions: e.g. lead poisoning
8. pseudopapilledema (anomalous elevation of the optic nerve head) associated with hyperopia and drusen. Retinal venous pulsations are usually present. Especially deceptive when a patient with migraines has pseudopapilledema: treat the H/A
9. malignant hypertension: may produce H/A & bilateral optic disc edema which can be indistinguishable from papilledema. May also produce hypertensive encephalopathy (*see page 73*). Check BP in all IIH suspects
10. meningeal carcinomatosis
11. Guillain-Barré syndrome: CSF protein is usually elevated (*see page 66*)
12. following head trauma

EVALUATION RECOMMENDATIONS

Most tests are intended to rule out conditions that may mimic IIH:

1. cerebral imaging: cerebral CT or MRI (*see below*) scan without and with contrast
2. LP:
   A. measure opening pressure **(OP)** with patient in lateral decubitus position
   B. CSF analysis to rule-out infection (e.g. fungus, TB or Lyme disease), inflammation (e.g. sarcoidosis, SLE) or neoplasm (e.g. carcinomatous meningitis)
      1. protein/glucose

2. cell count
3. routine & fungal cultures
4. cytology if suspicion of carcinomatous meningitis
3. routine labs: CBC, electrolytes, PT/PTT
4. W/U for sarcoidosis (*see page 71*) or SLE if other findings suggestive (e.g. cutaneous nodules, hypercoagulable state…)
5. neuro-ophthalmologic evaluation is recommended. Includes: visual field testing using quantitative perimetry, with evaluation of size of blind spot, slit-lamp examination ± fundus photographs
6. check BP to R/O malignant HTN → hypertensive encephalopathy (*see page 716*)

CT

CT without and with IV contrast is usually adequate to R/O intracranial mass, but may miss cases of dural sinus thrombosis. MRI & MRV are preferred.

MRI

Intracranial abnormalities are usually absent or minimal (slit ventricles, empty sella in 30-70%). However, **intraorbital findings** may be more substantial and include[671]:

1. flattening of the posterior sclera: occurs in 80%
2. enhancement of the prelaminar optic nerve: in 50%
3. distention of the perioptic subarachnoid space: in 45%
4. vertical tortuosity of the orbital optic nerve: in 40%
5. intraocular protrusion of the prelaminar optic nerve: in 30%

Venography

Conventional venography or MR venography **(MRV)** to rule-out dural sinus or venous thrombosis.

TREATMENT AND MANAGEMENT

NATURAL HISTORY

Spontaneous resolution is common, sometimes within months, but usually after ≈ 1 year. Papilledema persists in ≈ 15%. Permanent visual loss occurs in 2-

24%. Persistent H/A may occur in some. Recurs in ≈ 10% after initial resolution[671].

INTERVENTIONS

Studies are often difficult to interpret especially since spontaneous remission is common.

1. all patients must have repeated thorough ophthalmologic exams (*see above*)
2. stop possible offending drugs
3. weight loss: a weight loss of 6% usually results in complete resolution of papilledema[678]. However, resolution may be too slow for acutely threatened vision. Weight loss is also associated with reduction of other health risks of obesity. Symptoms recur if the weight is regained
   A. dieting: 679rarely accomplished or sustained
   B. bariatric surgery: gastric bypass, laparoscopic banding…
4. treatment of asymptomatic IIH patients is controversial as there is no reliable predictor for visual loss. Close follow up with serial formal visual field evaluation is necessary. Intervention is recommended in unreliable patients, or whenever visual fields deteriorate. It is possible to lose vision without H/A or papilledema
5. most cases remit by 6-15 weeks, however relapse is common
6. medical treatment
   A. fluid and salt restriction
   B. diuretics (slows CSF production)
      1. carbonic anhydrase **(CA)** inhibitors:
         a. acetazolamide (Diamox®): ***Rx*** start at 125-250 mg PO q 8-12 hrs, or long acting Diamox Sequels® 500 mg PO BID. Increase by 250 mg/day until symptoms improve, side effects occur, or 2 gm/day reached. **SIDE EFFECTS:** (in high doses): acral paresthesias, nausea, metabolic acidosis, altered taste, renal calculi, drowsiness. Rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis. ✖ Contraindicated with allergy to sulfa or a history of renal calculi
         b. methazolamide (Neptazane®): better tolerated but less effective. ***Rx*** 50-100 mg PO BID-TID. **SIDE EFFECTS:** similar to acetazolamide
         c. topiramate (Topamax®): anticonvulsant with secondary

inhibition of CA. ***Rx*** 200 mg PO BID. **SIDE EFFECTS:** Similar to acetazolamide, but can be used in sulfa allergic patients

2. furosemide (Lasix®)
   a. start: 160 mg per day in adults, adjust per symptoms and eye exam (not to CSF pressure)
   b. if ineffective, double (320 mg/day)
   c. monitor K^+ levels and supplement as needed

C. if ineffective, add steroids (options: dexamethasone (Decadron®) 12 mg/day, prednisone 40-60 mg/day, or methylprednisolone 250 mg IV q 6 hrs). May ↑ CSF resorption in cases of inflammation or venous thrombosis. Can be used as temporizing agents for patients awaiting surgery. A reduction in symptoms should occur by 2 weeks, after which time the steroid should be tapered over 2 weeks. Long-term use is not recommended due to, among other things, associated weight gain

7. surgical therapy[267 (p 250-3)] only for cases refractory to above, or where visual loss is progressive or is severe initially or unreliable patient:
   A. serial LPs until remission (25% remit after 1st LP[680]): remove up to 30 ml to halve OP, perform qod until OP < 20 cm H_2O, then decrease to q wk (no patient who had remission by 2nd LP had OP > 350 on 1st LP). Use a large gauge needle (e.g. 18 Ga) which may help promote a post-LP CSF leak into subcutaneous tissues. LPs may be difficult in obese patients. Revisions may be required in up to 50%. **SIDE EFFECTS:** include sciatica from nerve root irritation, acquired cerebellar tonsillar herniation (*see page 317*), spinal H/A (from intracranial hypotension)
   B. shunts
      1. lumbar shunt: usually lumboperitoneal (for insertion technique, *see page 213*). May be difficult in obese patient. May need a horizontal-vertical valve (*see page 317*) to prevent H/A from intracranial hypotension. Alternative: lumbopleural shunt
      2. other shunts may be used, especially when arachnoiditis precludes use of lumbar subarachnoid space, e.g.:
         • VP shunt: often difficult since the ventricles are frequently small or slit-like[681]. Stereotactic techniques may make this more technically feasible
         • cisterna magna shunt: may shunt to vascular system
   C. optic nerve sheath fenestration: *see below*
   D. obsolete treatment (presented for historical interest): subtemporal

(advocated by Dandy) or suboccipital decompression. Usually bilateral silver-dollar size craniectomies under temporalis muscle to floor of middle fossa, open dura, cover brain with absorbable sponge, close fascia and muscle water-tight, anticonvulsants were started due to risk of post-op seizures

8. interventional procedures: venous sinus stenting may be considered for refractory cases[682]
9. patients should be followed at least two years (with repeat imaging, e.g. MRI) to R/O occult tumor

Optic nerve sheath fenestration (ONSF)[683-685]

Generally better for protection of vision and reversal of papilledema than for other symptoms (e.g. H/A). Performed via medial or less commonly a lateral orbitotomy or transconjunctival medial approach. May reverse or stabilize visual deterioration[686] and sometimes (but not always) lowers ICP (by continued CSF filtration) and may protect the contralateral eye (if not, contralateral ONSF must be performed). Has succeeded in cases where visual loss progressed after LP shunting[687], possibly due to poor communication between orbital and intracranial subarachnoid spaces. **Side effects:** potential adverse include: pupillary dysfunction, peripapillary hemorrhage, chemosis, chorioretinal scarring[688], diplopia (usually self-limited) from medial rectus disruption. Repeat fenestration is needed in 0-6%[671].

Management recommendations for specific situations

Weight loss should be attempted in all.

1. IIH patients with H/A and no visual loss: medical therapy to control ↑ ICP and H/A. ONSF <u>not</u> recommended. Shunting is an option if medical management fails
2. IIH with visual loss without H/A:
   A. mild visual loss: acetazolamide 500-1500 mg/d, follow-up q 2 weeks
   B. moderate visual loss: acetazolamide 2000-3000 mg/d, follow-up q week
   C. severe visual loss, moderate visual loss that doesn't respond to acetazolamide, or optic disc at risk:
      1. methylprednisolone 250 mg IV q 6 hrs + acetazolamide 1000 mg PO BID
      2. if no improvement: ONSF. Consider shunt if ICP > 300 mm H_2O

3. IIH with visual loss AND H/A: for patients with surgical indications, either surgical procedure is appropriate. Shunting may relieve both problems simultaneously. ONSF may be more reliable to relieve the visual problems (the failure rate may be lower than the shunt malfunction rate) but is not as good for the H/A
4. IIHWOP: symptomatic treatment for H/A, diuretics
5. IIH in children and adolescents:
   A. may be seen with withdrawal of steroids used for asthma
   B. search for and correction of underlying etiology (offending drugs listed above, hypercalcemia, cancer…)
   C. acetazolamide has been used with success
6. IIH in pregnancy:
   A. women who first present with IIH during pregnancy: resolution of IIH following delivery is common
   B. women who become pregnant during therapy:
      1. 1st trimester: observation, limitation of weight gain, serial LPs. ✖ Acetazolamide should be avoided because of teratogenicity
      2. 2nd & 3rd trimester: acetazolamide has been used safely, but involvement of high-risk obstetrician specialist is advised
7. pseudopapilledema (associated with drusen, etc., in the absence of IIH): no interventions[671]. Reassurance and H/A management are employed

21.9. Empty sella syndrome

Empty sella syndrome **(ESS)** can be “primary” or “secondary”.

PRIMARY EMPTY SELLA SYNDROME

Occurs in the absence of prior treatment of a pituitary tumor (medical, surgical or XRT). Herniation of the arachnoid membrane into the sella turcica[689] which can act as a mass, probably as a result of repeated CSF pulsation. The sella can become enlarged (see *Sella turcica*, page 138 for normal dimensions) and the pituitary gland may become compressed against the floor.

Frequent association: female sex (female:male ratio = 5:1), obesity and HTN. The frequency of intrasellar arachnoid herniation is higher in patients with pituitary tumors and in those with increased intracranial pressure for any reason (including idiopathic intracranial hypertension, *see page 713*) than in the general

population.

These patients usually present with symptoms that do not suggest an intrasellar abnormality including: headache (the most common symptom), dizziness, seizures… Occasionally patients may develop CSF rhinorrhea[690], deterioration of vision (acuity or field deficit resulting from kinking of optic chiasm due to herniation into the sella), or amenorrhea-galactorrhea syndrome.

Clinically evident endocrine disturbances are rare with primary ESS, however up to 30% have abnormal pituitary function tests, most commonly reduced growth hormone secretion following stimulation. Mild elevation of prolactin **(PRL)** and reduction of ADH may occur, probably from compression of the stalk. These patients show a normal PRL rise with TRH stimulation (whereas patients with prolactinomas do not).

Treatment: Surgical treatment is usually not indicated, except in the case of CSF rhinorrhea. In this setting, it is necessary to determine if there is increased ICP, and if so, if there is an identifiable cause. Simple shunting for hydrocephalus runs the risk of producing tension pneumocephalus from air drawn in through the former leak site. This may necessitate transsphenoidal repair with simultaneous external lumbar drainage, to be converted to a permanent shunt shortly thereafter. Hyperprolactinemia may be treated e.g. with bromocriptine (*see page 651*) if it interferes with gonadal function.

SECONDARY EMPTY SELLA SYNDROME

Entities associated with secondary empty sella syndrome:

1. following trauma[691]
2. after successful transsphenoidal removal or XRT for a pituitary tumor[691]
3. any cause of increased intracranial pressure, including: idiopathic intracranial hypertension (pseudotumor cerebri), Chiari malformation

Often presents with visual deterioration due to herniation of the optic chiasm into the empty sella. There may be hypopituitarism from the underlying cause.

Visual deterioration may be treated with chiasmopexy (propping up the chiasm) usually by transsphenoidal approach and packing the sella with fat, muscle or cartilage.

21.10. Tumor markers

TUMOR MARKERS USED HISTOLOGICALLY IN NEUROSURGERY

GLIAL FIBRILLARY ACIDIC PROTEI ***(GFAP)***

Polypeptide, MW = 49,000 Daltons. Although the presence of GFAP usually indicates astroglial origin, it may occasionally be seen in oligodendrogliomas, ependymomas, and choroid plexus papillomas[197 p (30-1)]. GFAP is only rarely found outside the CNS (in nonmyelinated Schwann cells, epithelium of the lens, hepatic Kupffer cells…). Thus, the presence of GFAP in a tumor found in the CNS is usually taken as good evidence for glial origin of the tumor. GFAP also occurs in normal brain parenchyma.

S-100 PROTEIN

A low molecular weight (21,000 Daltons) calcium-binding protein. Used on tissue microscopy for pathology. May participate in regulation of microtubule assembly. In CNS tumors, the distribution is similar to GFAP, but it is not as specific as GFAP (may be found in other cell types such as stellate cells of the adenohypophysis, chondrocytes)[197 p (34-5)], melanomas. In the peripheral nervous system, it is localized in Schwann cells. May be helpful in distinguishing Schwann cells from perineurial cells.

Clinically has been measured in serum (*see below*).

CYTOKERATIN (HIGH & LOW MOLECULAR WEIGHT)

Stains epithelial cells. Most primary brain tumors do not stain positive. Supports the diagnosis of carcinoma. May help distinguish metastatic tumors (when a positive stain occurs) from primary CNS tumors.

MIB-1 (AKA MONOCLONAL MOUSE ANTI-HUMAN ***KI-67*** *ANTIBODY)*

The Ki-67 antigen is expressed in all phases of the cell cycle except G0. A valuable marker of cell proliferation, but can only be used with fresh-frozen specimens. MIB-1 is a monoclonal antibody developed using recombinant parts of the Ki-67 protein as an immunogen, and can be used on paraffin-embedded sections of fixed tissue. Cells leaving the G_0/G_1-phase and entering the S-phase (performing DNA synthesis) stain positive with MIB-1 immunohistochemical stain. A high MIB-1 labeling index denotes high mitotic activity which often correlates with degree of malignancy. Most often used in lymphomas and breast cancer. For use in astrocytomas *see page 596*, for meningiomas *see page 616*.

Table 10-75 Immunohistochemical staining patterns for nervous system tumor masses of epithelioid cells*

<table>
<tr><th rowspan="2">Neoplasm</th><th colspan="6">Immunohistochemical stain response† ‡</th></tr>
<tr><th>GFAP</th><th>CAM5.2</th><th>EMA</th><th>S-100</th><th>CgA</th><th>Syn</th></tr>
<tr><td>oligodendroglioma</td><td>+</td><td rowspan="2">–</td><td>–</td><td rowspan="4">+</td><td rowspan="2">–</td><td></td></tr>
<tr><td>ependymoma</td><td></td><td rowspan="2"></td><td>–</td></tr>
<tr><td>choroid plexus papilloma</td><td rowspan="8">–</td><td rowspan="5">+</td><td></td><td>+</td></tr>
<tr><td>chordoma</td><td rowspan="4">+</td><td rowspan="2">–</td><td rowspan="2">–</td></tr>
<tr><td>craniopharyngioma</td><td rowspan="2">–</td></tr>
<tr><td>carcinoma</td><td></td><td></td></tr>
<tr><td>pituitary adenoma</td><td rowspan="3"></td><td rowspan="2">+</td><td rowspan="2">+</td></tr>
<tr><td>paraganglioma</td><td rowspan="2"></td><td>–</td></tr>
<tr><td>meningioma</td><td>+</td><td rowspan="3">–</td><td rowspan="2">–</td></tr>
<tr><td>melanoma</td><td rowspan="2">–</td><td rowspan="2">–</td><td>+</td></tr>
<tr><td>hemangioblastoma</td><td></td><td></td><td></td></tr>
</table>

* reproduced from McKeever, P E, Immunohistochemistry of the Nervous System, in Dobbs, D J Diagnostic Immunohistochemistry, Churchill Livingstone, NY, © 2002

† abbreviations: GFAP = glial fibrillary acidic protein, EMA = epithelial membrane antigen, CAM5.2 = cytokeratin CAM5.2, CgA = chromogranin A, syn = synaptophysin

Neuroendocrine stains

Includes:

1. chromogranin: stains for neural crest derivatives, viz. pituitary adenomas, paragangliomas, neuroendocrine tumors
2. synaptophysin: stains neuronal and pineal tumors, PNET & medulloblastomas
3. neuron specific enolase **(NSE)**: very sensitive but not specific for neuroendocrine

Metastases that are positive for neuroendocrine stains include: small-cell carcinoma of the lung, malignant pheochromocytoma, Merkel cell tumor. Metastatic small-cell tumors to the brain staining positive for neuroendocrine stains are almost all due to lung.

Staining patterns[692]

An individual tumor may lack a marker that is typically representative of its type. Therefore, a positive stain is more significant than a negative stain. General staining patterns are shown in *Table 10-75*.

Tumor markers used clinically

Human chorionic gonadotropin ***(HCG)***

A glycoprotein, MW = 45,000. Secreted by placental trophoblastic epithelium. Beta chain (ß-hCG) is normally present only in the fetus or in gravid or postpartum females, otherwise it indicates disease. Classically associated with choriocarcinoma (uterine or testicular), also found in patients with embryonal cell tumors, teratocarcinoma of testis, and others.

CSF ß-hCG is 0.5-2% of serum ß-hCG in non-CNS tumors. Higher levels are diagnostic of cerebral mets from uterine or testicular choriocarcinoma, or primary choriocarcinoma or embryonal cell carcinoma of pineal (*see page 691*) or suprasellar region.

ALPHA-FETOPROTEIN

Alpha-fetoprotein **(AFP)** is a normal fetal glycoprotein (MW = 70,000) initially produced by the yolk sac, and later by the fetal liver. It is found in the fetal circulation throughout gestation, and drops rapidly during the first few weeks of life, reaching normal adult levels by age 1 yr. It is detectable only in trace amounts in normal adult males or nonpregnant females. It is present in amniotic fluid in normal pregnancies, and is detectable in maternal serum starting at ≈ 12-14 weeks gestation, increasing steadily throughout pregnancy until ≈ 32 weeks[693].

Abnormally elevated serum AFP may occur in Ca of ovary, stomach, lung, colon, pancreas, as well as in cirrhosis or hepatitis and in the majority of gravid women carrying a fetus with an open neural tube defect (see *Prenatal detection of neural tube defects*, page 245). Serum AFP > 500 ng/ml usually means primary hepatic tumor.

CSF-AFP is elevated in some pineal region germ-cell tumors (*see page 692*). 16-25% of patients with testicular tumors get cerebral mets and elevated CSF AFP levels are reported in some.

CARCINOEMBRYONIC ANTIGEN ***(CEA)***

A glycoprotein, MW = 200,000. Normally present in fetal endodermal cells. Originally described with colorectal adeno-Ca, now known to be elevated in many malignant and nonmalignant conditions (including cholecystitis, colitis, diverticulitis, hepatic involvement from any tumor, with 50-90% of terminal patients having elevation).

CSF CEA: levels > 1 ng/ml are reported with leptomeningeal spread of lung Ca (89%), breast Ca (60-67%), malignant melanoma (25-33%), and bladder Ca. May be normal even in CEA secreting cerebral mets if they don’t communicate with the subarachnoid space. Only carcinomatous meningitis from lung or breast

Ca consistently elevates CSF CEA in the majority of patients.

S-100 PROTEIN

Serum S-100 protein levels rise after head trauma, and possibly after other insults to the brain. Levels may also be elevated in Creutzfeldt-Jakob disease (*see page 363*).

21.11. Neurocutaneous disorders

Formerly called **phakomatoses**. Neurocutaneous disorders **(NCD)** are a group of conditions, each with unique neurologic findings and benign cutaneous lesions (NB: both skin and the CNS derive embryologically from ectoderm), usually with dysplasia of other organ systems (often including the eyes). With the exception of ataxia-telangiectasia (not discussed here) all exhibit autosomal dominant inheritance. There is also a high rate of spontaneous mutations. These syndromes should be kept in mind in a pediatric patient with a tumor, and other stigmata of these syndromes should be sought.

NCDs that are more likely to come to the attention of the neurosurgeon:

1. neurofibromatosis: *see below*
2. tuberous sclerosis: *see page 725*
3. von Hippel-Lindau disease: *see page 667*
4. Sturge Weber syndrome: *see page 726*
5. racemose angioma (Wyburn-Mason syndrome): midbrain and retinal AVMs

21.11.1. Neurofibromatosis

Neurofibromatosis **(NFT)** is the most common of the NCDs. There are as many as 6 distinct types, the two most common of which (NF1 & NF2) are compared in *Table 21-76* (variant forms also occur).

Schwannoma vs. neurofibroma: While similar in many ways, these tumors differ histologically. **Schwannomas** (nee: neurilemmomas) arise from schwann cells which produce myelin. **Neurofibromas** consist of neurites (axons or dendrites of immature or developing neurons), Schwann's cells, and fibroblasts within a collagenous or myxoid matrix. In contrast to shwannomas which

displace axons (centrifugal), neurofibromas are unencapsulated and engulf the nerve of origin (centripetal). Neurofibromas may occur as solitary lesions, or, may be multiple as part of NF1 in the setting of which there is potential for malignant transformation. Both tumors have Antoni A (compact) and Antoni B (loose) fibers, but neurofibromas tend to have more Antoni B fibers. A patient ≤ 30 years age with a vestibular schwannoma is at increased risk of having NF2.

Table 21-76 Comparison of neurofibromatosis 1 &2[694]

current designation →	Neurofibromatosis 1 (NF1)	Neurofibromatosis 2 (NF2)
see page	723	724
alternate term	von Recklinghausen’s	bilateral acoustic NFT AKA MISME syndrome
obsolete term	peripheral NFT	central NFT
U.S. prevalence	100,000 people	≈ 3000 people
incidence	1/3000 births	1 in 40,000
inheritance	AD	AD
sporadic occurrence	30-50%	> 50%
gene locus	17 (17q11.2)	22 (22q12.2)
gene product	neurofibromin	schwannomin (merlin)
vestibular schwannomas (VS)	almost never bilateral	bilateral VSs are the hallmark
cutaneous schwannomas	no	70%
Lisch nodules	very common	not associated
cataracts	not associated	60-80%
skeletal anomalies	common	not associated
pheochromocytoma	occasional	not associated
MPNST*	≈ 2%	not associated
associated intramedullary spinal cord tumors	astrocytoma	ependymoma
intellectual impairment	associated	not associated

* malignant peripheral nerve sheath tumor

Neurofibromatosis 1 (NF1 AKA von Recklinghausen’s disease[695])

Clinical features

More common than NF2, representing > 90% of cases of neurofibromatosis.

Diagnostic criteria: Are shown in *Table 21-77*[696].

Associated conditions:

1. Schwann-cell tumors on any nerve (but bilateral VSs are virtually nonexistent)
2. spinal and/or peripheral-nerve neurofibromas
3. multiple skin neurofibromas
4. aqueductal stenosis: *see page 241*
5. macrocephaly: secondary to aqueductal stenosis and hydrocephalus, increased cerebral white matter
6. intracranial tumors: hemispheric astrocytomas are the most common, solitary or multicentric meningiomas (usually in adults). Gliomas associated with NF1 are usually pilocytic astrocytomas. Brain stem astrocytomas include both contrast-enhancing pilocytic lesions and those that are non-enhancing and radiologically diffuse
7. unilateral defect in superior orbit → pulsatile exophthalmos
8. neurologic or cognitive impairment: 30-60% have mild learning disabilities
9. kyphoscoliosis (seen in 2-10%, often progressive which then requires surgical stabilization)
10. visceral manifestations from involvement of autonomic nerves or ganglia within the organ. Up to 10% of patients have abnormal gastrointestinal motility/neuronal intestinal dysplasia related to neuronal hyperplasia within submucosal plexus
11. ≈ 20% develop plexiform neurofibromas: tumors from multiple nerve fascicles that grow along the length of the nerve. Almost pathognomonic for NF1[697]
12. syringomyelia
13. malignant tumors that have increased frequency in NFT: neuroblastoma, ganglioglioma, sarcoma, leukemia, Wilm's tumor, breast cancer[698]
14. pheochromocytoma: is occasionally present
15. "unidentified bright objects" (UBOs) on brain or spinal MRI in 53-79% of patients (bright on T2WI, isointense on T1WI) that may be hamartomas, heterotopias, foci of abnormal myelination or low grade tumors[699]. Tend to resolve with age

Table 21-77 Diagnostic criteria for NF1[696]

Two or more of the following:
• ≥ 6 **café au lait spots***, each ≥ 5 mm in greatest diameter in prepubertal individuals, or ≥ 15 mm in greatest diameter in postpubertal patients
• ≥ 2 neurofibromas of any type, or one plexiform neurofibroma (neurofibromas are usually not evident until age 10-15 yrs). May be painful
• freckling (hyperpigmentation) in the axillary or intertriginous (inguinal) areas
• optic glioma: *see below*• ≥ 2 Lisch nodules: pigmented iris hamartomas that appear as translucent yellow/brown elevations that tend to become more numerous with age
• distinctive osseous abnormality, such as <u>sphenoid dysplasia</u> or thinning of long bone cortex with or without pseudarthrosis (e.g. of tibia or radius)
• a first degree relative (parent, sibling or off-spring) with NF1 by above criteria

* café au lait spots: hyperpigmented oval light brown skin macules (flat). May be present at birth, increase in number and size during 1st decade. Are present in > 99% of NF1 cases. Rare on face

Genetics

Simple autosomal dominant inheritance with variable expressivity but almost 100% penetrance after age 5 years. The NF1 gene is on chromosome 17q[11].2 which codes for neurofibromin[700] (neurofibromin is a negative regulator of the Ras oncogene). Loss of neurofibromin as in NF1 results in elevation of growth-promoting signals. The spontaneous mutation rate is high, with 30-50% of cases representing new somatic mutations[701].

Counselling: prenatal diagnosis is possible by linkage analysis only if there are 2 or more affected family members[700]. 70% of NF1 gene mutations can be detected.

Management

- optic gliomas
  - A. unlike optic gliomas in the absence of NFT, these are rarely chiasmal (usually involving the nerve), are often multiple, and have a better prognosis
  - B. most are non progressive, and should be followed ophthalmologically and with serial imaging (MRI or CT)
  - C. surgical intervention probably does not alter visual impairment. Therefore, surgery is reserved for special situations (large disfiguring tumors, pressure on adjacent structures…)
- other neural tumors in patients with NF1 should be managed in the same manner as in the general population

A. focal, resectable, symptomatic lesions should be surgically removed
B. intracranial tumors in NF1 may often be unresectable, and in these cases chemotherapy and/or radiation therapy may be appropriate, with surgery reserved for cases with increasing ICP
C. when malignant degeneration is suspected (rare, but incidence of sarcomas and leukemias is increased), biopsy with or without internal decompression may be indicated

NEUROFIBROMATOSIS 2 (NF2 AKA BILATERAL ACOUSTIC NFT[702])

AKA MISME syndrome (acronym for: Multiple Inherited Schwannomas, Meningiomas, and Ependymomas).

CLINICAL

Diagnostic criteria: Are shown in *Table 21-78*[703].

Other clinical features:

1. seizures or other focal deficits
2. skin nodules, dermal neurofibromas, café au lait spots (less common than in NF1)
3. multiple intradural spinal tumors are common (less common in NF1)[704]: including intramedullary (especially ependymomas) and extramedullary (schwannomas, meningiomas…)
4. retinal hamartomas
5. antigenic nerve growth factor is increased (does not occur with NF1)
6. despite its name, is not associated with neurofibromas

Two subtypes[703]:

1. the more common, severe form with younger age of onset (2nd to 3rd decade), with rapid progression of hearing loss and multiple associated tumors
2. milder form, presents later in life, with slower deterioration in hearing and fewer associated tumors

Table 21-78 Diagnostic criteria for NF2[703]

Definite diagnosis if either:

1. bilateral vestibular schwannomas (VS) on imaging (MRI or CT) or
2. a first degree relative (parent, sibling or off-spring) with NF2 and either:
   A. unilateral VS at age < 30 years or
   B. any two of the following: meningioma, schwannoma (including spinal root), glioma (includes astrocytoma, ependymoma), posterior subcapsular lens opacity

Probable diagnosis if either:

1. unilateral VS at age < 30 and any of the following: meningioma, schwannoma, glioma, posterior subcapsular lens opacity or
2. multiple meningiomas and either of the following: schwannoma, glioma, or posterior lens opacity

Genetics

Autosomal dominant inheritance. NF2 is due to a mutation at chromosome 22q[12].2 which results in the inactivation of schwannomin (AKA merlin, a semi-acronym for moesin-, ezrin-, and radixin-like proteins), a tumor suppression peptide.

Management considerations

- bilateral vestibular schwannomas:
  - chance of preserving hearing is best when tumor is small. Thus, one should attempt to remove smaller tumor. If hearing is serviceable in that ear after surgery, then consider removing the second tumor, otherwise follow the second tumor as long as possible and perform a subtotal removal in an attempt to prevent total deafness
  - stereotactic radiosurgery therapy may be a treatment option
- most NF2 patients will become deaf at some time during their life
- prior to surgery, obtain MRI of cervical spine to R/O intraspinal tumors that may cause cord injuries during other operations
- NB: pregnancy may accelerate the growth of eighth nerve tumors

21.11.2. Tuberous sclerosis complex

Key concepts:

- autosomal dominant. Incidence: 1 in 6K-10K live births
- clinical triad: seizures, mental retardation and sebaceous adenomas
- typical CNS finding: subependymal nodule (“tuber”) - a hamartoma
- common associated neoplasm: subependymal giant cell astrocytoma
- 2 tumor suppressor genes: TSC1 (on chromosome 9q[34]) codes for hamartin, and TSC2 (on chromosome 16p[13]) encodes tuberlin
- CT shows intracerebral calcifications (usually subependymal)

Tuberous sclerosis complex **(TSC)**, AKA Bourneville's disease, is a neurocutaneous disorder characterized by hamartomas of many organs including the skin, brain, eyes and kidneys. In the brain, the hamartomas may manifest as cortical tubers, glial nodules located subependymally or in deep white matter, or giant cell astrocytomas. Associated findings include pachygyria or microgyria.

EPIDEMIOLOGY/GENETICS

Incidence: 1 in 6,000-10,000 live births[10]. Point prevalence: 10.6 per 100,000 persons (from Rochester, MN[705]).

Autosomal dominant inheritance, however spontaneous mutation is common. Two distinct tumor suppressor genes have been identified: TSC1 (located on chromosome 9q[34]) codes for hamartin, and TSC2 (on chromosome 16p[13]) codes for tuberlin.

Genetic counseling for parents with one affected child: 1-2% chance of recurrence,

DIAGNOSIS

Diagnostic criteria are shown in *Table 21-79*.

In the infant, the earliest finding is of "ash leaf" macules (hypomelanotic, leaf shaped) that are best seen with a Wood's lamp. Infantile myoclonus may also occur.

In older children or adults, the myoclonus is often replaced by generalized tonic-clonic or partial complex seizures which occurs in 70-80%. Facial adenomas are not present at birth, but appear in > 90% by age 4 yrs (these are not really adenomas of the sebaceous glands, but are small hamartomas of cutaneous nerve elements that are yellowish-brown and glistening and tend to arise in a butterfly malar distribution usually sparing the upper lip).

Retinal hamartomas occur in ≈ 50% (central calcified hamartoma near the disc or a more subtle peripheral flat salmon-colored lesion). A distinctive depigmented iris lesion may also occur.

Plain skull x-rays

May show calcified cerebral nodules.

Table 21-79 Diagnostic criteria of tuberous sclerosis complex[706]

• **TSC**: diagnosis requires 2 major criteria, or 1 major and 2 minor criteria • **Probable TSC**: 1 major + 1 minor

• **Possible TSC**: 1 major or 2 minor
Major criteria
• cutaneous manifestations: facial angiofibroma, ungual fibroma, > 3 hypomelanotic macules, shagreen patch • brain and eye lesions: cortical tuber, subependymal nodules, subependymal giant cell astrocytoma, multiple retinal nodular hamartomas • tumors in other organs: cardiac, rhabdomyoma, lymphangioleiomyomatosis, renal angiomyolipoma
Minor criteria
• rectal polyps • pits in dental enamel • bone cysts • migration abnormalities of cerebral white matter • gingival fibromas • nonrenal hamartomas • achromic retinal patches • confetti skin lesions • multiple renal cysts

CT scan[707]

Intracerebral calcifications are the most common (97% of cases) and characteristic finding. Primarily located subependymally along the lateral walls of the lateral ventricles or near the foramina of Monro.

Low density lesions that do not enhance are seen in 61%. Probably represent heterotopic tissue or defective myelination. Most common in occipital lobe.

Hydrocephalus **(HCP)** may occur even without obstruction. In the absence of tumor, HCP is usually mild. Moderate HCP usually occurs only in the presence of tumor.

Subependymal nodules are usually calcified, and protrude into the ventricle ("**candle guttering**" the appearance on pneumoencephalography).

Paraventricular tumors (mostly giant cell astrocytomas, *see below*) are essentially the only enhancing lesion in TSC.

PATHOLOGY

Subependymal nodules ("tubers") are benign hamartomas that are almost always calcified, and protrude into the ventricles.

Giant cell astrocytoma: a transformation lesion. Almost always located at the foramen of Monro. Occurs in 5-15% of patients with TSC[708]. Histology shows fibrillary areas alternating with cells containing generous amounts of eosinophilic cytoplasm. Areas of necrosis and abundant mitotic figures may be seen, but are not associated with the typical malignant aggressiveness that these features usually denote[709].

TREATMENT

Paraventricular tumors should be followed, and removed only if they are symptomatic. The transcallosal route is recommended by some.

Infantile myoclonus may respond to steroids. Seizures are treated with AEDs.

Surgery for intractable seizures may be considered when a particular lesion is identified as a seizure focus. Better seizure control, not cure, is the goal in TSC.

21.11.3. Sturge–Weber syndrome

Key concepts:

> • cardinal signs: 1) localized cerebral cortical atrophy and calcifications, 2) ipsilateral port-wine facial nevus (usually in distribution of V_1)
> • contralateral seizures usually present
> • plain skull films classically show “tram-tracking” (double parallel lines)

AKA encephalotrigeminal angiomatosis. A neurocutaneous disorder consisting of:

1. cardinal features:
   A. localized cerebral cortical atrophy and calcifications (especially cortical layers 2 and 3, with a predilection for the occipital lobes):
      1. calcifications appear as curvilinear double parallel lines (“**tram-tracking**”) on plain x-rays
      2. cortical atrophy usually causes contralateral hemiparesis, hemiatrophy, and homonymous hemianopia (with occipital lobe involvement)

   B. ipsilateral port-wine facial nevus (**nevus flammeus**) usually in distribution of 1st division of trigeminal nerve (rarely bilateral)
2. other findings that may be present:
   A. ipsilateral exophthalmos and/or glaucoma, coloboma of the iris
   B. oculomeningeal capillary hemangioma
   C. convulsive seizures: contralateral to the facial nevus and cortical atrophy. Present in most patients starting in infancy
   D. retinal angiomas

GENETICS

Most cases are sporadic. Other cases are suggestive of recessive inheritance, with chromosome 3 being implicated.

TREATMENT

Treatment is supportive. Anticonvulsants are used for seizures. Lobectomy or hemispherectomy may be needed for refractory seizures. XRT: complications are common and benefits are lacking. Laser surgery for the cutaneous nevus is disappointing; better results obtain from masking the nevus with a skin colored tattoo.

21.11.4. Neurocutaneous melanosis (NCM)

BACKGROUND

1. a rare, congenital, nonheritable phakomatosis in which large or numerous congenital melanocytic nevi are associated with benign and/or malignant melanocytic tumors of the leptomeninges[710]
2. pathogenesis: neuroectodermal defect during morphogenesis involving melano-blasts of skin and pia mater originating from neural crest cells[710]

CLINICAL FEATURES

1. two-thirds of patients with NCM have giant congenital melanocytic nevi[A][710]
2. one-third have numerous lesions[A] without a single giant lesion[710]
3. virtually all have large cutaneous melanocytic (pigmented) nevi located on the posterior torso[711]
4. neurologic manifestations: usually before age 2 years. Signs of intracranial hypertension (lethargy, vomiting…), focal seizures, motor deficits or aphasia[710]
5. hydrocephalus: in almost 66%. Usually due to obstruction of CSF flow or reduced absorption as a result of thickened leptomeninges[710]

A. pigmented nevi that are large, hairy, or both. The chances that nevi represents NCM is higher when the nevi are located on head, posterior neck or paravertebral)

Clinical diagnostic criteria[712]

1. large or multiple congenital melanocytic nevi with meningeal melanosis or melanoma
2. absence of cutaneous melanoma, except in patients with benign meningeal lesions (i.e. must rule-out meningeal metastases from cutaneous melanoma)
3. no evidence of meningeal melanoma, except in patients with benign cutaneous lesions

Associated conditions

NCM is sometimes associated with

1. neurocutaneous syndromes[710]
   A. Sturge-Weber syndrome (*see page 726*)
   B. von Recklinghausen's neurofibromatosis (NF1) (*see page 723*)
2. posterior fossa cystic malformations: (e.g. Dandy Walker malformation (*see page 240*)) occurs in up to 10%. These cases have worse prognosis due to malignant transformation[710]
3. intraspinal lipoma and syringomyelia[710]

Diagnostic testing

1. MRI: T_1 and T_2 signal shortening produced by melanin. IV gadolinium may demonstrate enhancement of tumor-infiltrated meninges[710]
2. histological exam of CNS lesions shows leptomeningeal melanosis (benign) which develops from the melanocytes of the pia matter. Melanoma (malignant) occurs in 40-62% of cases but distinction has little prognostic significance because of the poor outcome of the symptomatic NCM patient even in the absence of melanoma[710]

Management

The benefit of resecting skin lesions is questionable in the presence of leptomeningeal lesions[713]. NCM appears refractory to radiation therapy and chemotherapy[713]

Neurosurgical involvement is usually limited to[712]:

1. shunting for hydrocephalus
2. palliative operative decompression if early in the course

3. biopsy for tissue diagnosis in questionable cases

PROGNOSIS

1. when neurological signs are present, prognosis is poor regardless of whether or not malignancy is present
2. > 50% of patients die within 3 years after the first neurologic manifestation[710]

21.12. Tumors of the spine and spinal cord

15% of primary CNS tumors are intraspinal (the intracranial:spinal ratio for astrocytomas is 10:1; for ependymomas it's 3-20:1)[714]. There is disagreement over the prevalence, prognosis, and optimal treatment. Most primary CNS spinal tumors are benign (unlike the case with intracranial tumors). Most present by compression rather than invasion[715].

TYPES OF SPINAL TUMORS

May be classified in 3 groups. Although metastases may be found in each category, they are usually extradural. Frequencies quoted below are from a general hospital, extradural lesions are less common in neurosurgical clinics because of relative exclusion of extradural lymphomas, metastatic Ca, etc.:

1. **extradural (ED)** (55%): arise outside cord in vertebral bodies or epidural tissues
2. **intradural extramedullary (ID-EM)** (40%): arise in leptomeninges or roots. Primarily meningiomas and neurofibromas (together = 55% of ID-EM tumors)
3. **intramedullary spinal cord tumors (IMSCT)** (5%): arise in SC substance. Invade and destroy tracts and grey matter, *see page 730*

DIFFERENTIAL DIAGNOSIS: SPINE & SPINAL CORD TUMORS

See also *Myelopathy* on page 1185 for a list including nonneoplastic causes of spinal cord dysfunction (e.g. spinal meningeal cyst, epidural hematoma, transverse myelitis…).

1. extradural spinal cord tumors (55%): arise in vertebral bodies or epidural tissues

A. metastatic: comprise the majority of ED tumors
   1. most are osteolytic (cause bony destruction): see *Spinal epidural metastases*, page 742. Common ones include:
      a. lymphoma: most cases represent spread of systemic disease (secondary lymphoma); some cases may be primary (*see below*)
      b. lung
      c. breast
      d. prostate
   2. metastases that may be osteoblastic:
      a. in men: prostate Ca is the most common
      b. in women: breast Ca is the most common
B. primary spinal tumors (very rare)
   1. chordomas: *see page 675*
   2. osteoid osteoma: *see page 736*
   3. osteoblastoma: *see page 736*
   4. **aneurysmal bone cyst (ABC)**: an expansile tumor-like osteolytic lesion consisting of a highly vascular honeycomb of blood-filled cavities separated by connective tissue septa, surrounded by a thin cortical bone shell which may expand. Comprise 15% of spine tumors[716]. Etiology is controversial. May arise from preexisting tumor (including: osteoblastoma, giant cell tumor, fibrous dysplasia, chondrosarcoma) or following acute fracture. In spine, there is a tendency to involve primarily the posterior elements. Peak incidence is in 2nd decade of life. Treatment usually consists of intralesional curettage. High recurrence rate (25-50%) if not completely excised
   5. chondrosarcoma: a malignant tumor of cartilage. Lobulated tumors with calcified areas
   6. osteochondroma (chondroma): benign tumors of bone that arise from mature hyaline cartilage. Most common during adolescence. An enchondroma is a similar tumor arising within the medullary cavity
   7. vertebral hemangioma: *see page 738*
   8. **giant cell tumors (GCT)** of bone: AKA osteoclastoma (*see page 742*)
   9. giant cell (reparative) granuloma: AKA solid variant of ABC[717]. Related to GCT. Occurs primarily in mandible, maxilla, hands and feet, but there are case reports of spine involvement[717, 718]. Not a

true neoplasm - more of a reactive process. Treatment: curettage. Recurrence rate: 22-50%, treated with re-excision

10. brown tumor of hyperparathyroidism
11. osteogenic sarcoma: rare in spine

C. miscellaneous
1. plasmacytoma: *see* *page 741*
2. multiple myeloma: *see* *page 740*
3. **eosinophilic granuloma (EG)**: osteolytic defect with progressive vertebral collapse (EG is one cause of **vertebra plana** - *see* *page 1232*). C-spine is the most commonly affected region. Isolated EG associated with systemic conditions (Letterer-Siwe or Hand-Schüller-Christian disease) are treated with biopsy and immobilization. Collapse or neurologic deficit from compression may require decompression and/or fusion. Low-dose RTX may also be effective[719, 720]
4. Ewing's sarcoma: aggressive malignant tumor with a peak incidence during 2nd decade of life. Spine mets are more common than primary spine lesions. Treatment is mostly palliative: radical excision followed by RTX (very radiosensitive) and chemotherapy[721]
5. chloroma: focal infiltration of leukemic cells
6. angiolipoma: ≈ 60 cases reported in literature
7. neurofibromas: most are intradural, but some are extradural (*see* *page 735*), usually dilate neural foramen (dumbbell tumors)
8. Masson's vegetant intravascular hemangioendothelioma[722] (*see* *page 716*)

2. intradural extramedullary spinal cord tumors (40%)
   A. meningiomas: *see below*
   B. neurofibromas
   C. many lipomas are extramedullary with intramedullary extension
   D. miscellaneous: only ≈ 4% of spinal metastases involve this compartment
3. tumors that are usually intradural, but may be partly or wholly extradural:
   A. meningiomas: 15% of spinal meningiomas are extradural
   B. neurofibromas
4. intramedullary spinal cord tumors (5%): *see below*
   A. astrocytoma: 30% (*see* *page 731*)

B. ependymoma: 30% (*see page 731*) (including myxopapillary ependymoma, *see page 731*)

C. miscellaneous: 30%, includes:

1. malignant glioblastoma
2. dermoid. In addition to the general population, dermoids present in a delayed fashion following ≈ 16% of myelomeningocele **(MM)** closures[723]. An iatrogenic etiology has been debated[724], however a case of a congenital dermoid in a newborn with MM[725] indicates that the origin is not always from incompletely excised dermal elements at the time of MM closure
3. epidermoid
4. teratoma
5. lipoma
6. hemangioblastoma (*see page 732*)
7. neuroma (very rare intramedullary)
8. syringomyelia (not neoplastic)
9. extremely rare tumors
   a. lymphoma
   b. oligodendroglioma
   c. cholesteatoma
   d. intramedullary metastases: comprises only ≈ 2% of spinal mets

SPINAL MENINGIOMAS[726]

Epidemiology

Peak age: 40-70 years. Female:male ratio = 4:1 overall, but the ratio is 1:1 in the lumbar region. 82% thoracic, 15% cervical, 2% lumbar. 90% are completely intradural, 5% are extradural, and 5% both intra- and extra-dural. 68% are lateral to the spinal cord, 18% posterior, 15% anterior. Multiple spinal meningiomas occur rarely.

Clinical

Symptoms

	At onset	At time of first surgery
1. local or radicular pain:	42%	53%

2. motor deficits:	33%	92%
3. sensory symptoms:	25%	61%
4. sphincter disturbance:		50%

Signs prior to surgery (only 1 of 174 patients was intact)[726]

1. motor
   - A. pyramidal signs only: 26%
   - B. walks with aid: 41%
   - C. antigravity strength:17%
   - D. flexion-extension with gravity removed: 6%
   - E. paralysis: 9%
2. sensory
   - A. radicular: 7%
   - B. long tract: 90%
3. sphincter deficit: 51%

Outcome

Recurrence rate with complete excision is 7% with a minimum of 6 years follow-up (relapses occurred from 4 to 17 years post-op)[726].

SPINAL LYMPHOMA

1. epidural
   - A. metastatic or secondary lymphoma: the most common form of spinal lymphoma. Spinal involvement occurs in 0.1-10% of patients with non-Hodgkin's lymphoma
   - B. primary spinal epidural non-Hodgkin's lymphoma: rare. Completely epidural with no bony involvement. The existence of this entity is controversial, and some investigators feel that it represents extension of undetected retroperitoneal or vertebral body lymphoma. May have a better prognosis than secondary lymphoma[727]
2. intramedullary
   - A. secondary: *see page 732*
   - B. primary: very rare (*see below*)

21.12.1. Intramedullary spinal cord tumors

21.12.1.1. Types of intramedullary spinal cord tumors

The following list excludes metastases (*see below*) and lipomas (of questionable neo-plastic origin[728], and most are actually extramedullary intradural, *see below*).

1. astrocytoma (nonmalignant): 30%[A] (the most common intramedullary spinal cord tumors **(IMSCT)** outside the filum terminale[715]) tend to be eccentric
2. ependymoma: 30%A, tend to be more central, more uniform dense enhancement
3. miscellaneous: 30%, including:
   - A. malignant glioblastoma
   - B. dermoid
   - C. epidermoid (including iatrogenic from LP without stylet)[729, 730]
   - D. teratoma
   - E. hemangioblastoma (*see below*)
   - F. hemangioma
   - G. neuroma (very rarely intramedullary)
   - H. extremely rare tumors
     1. primary lymphoma (only 6 case reports, all non-Hodgkin type[731])
     2. oligodendroglioma, only 38 cases in world literature[732]
     3. cholesteatoma
     4. paraganglioma
     5. primarily spinal embryonal tumor ("spinal PNET") (*see page 685*)[530]
     6. pilomyxoid astrocytoma (*see page 606*)
     7. metastasis

A. in pediatrics, astrocytoma and ependymoma constitute 90% of IMSCT

Differential diagnosis

(also see DDx for *Myelopathy* on page 1185)

- neoplasm (tumor): (*see above* for list). **Enhancement**: 91% enhance[733]; of the 9% that do not, most were astrocytomas, 1 was a subependymoma; enhancement did not correlate with grade

- nonneoplastic lesions
  - vascular lesions (e.g. AVM): serpiginous linear flow-void. Spinal angiography may be useful[715]
  - demyelinating disease (e.g. multiple sclerosis):
    1. usually does not extend > 2 vertebral levels
    2. cord lesions in MS are most common in the cervical region
  - inflammatory myelitis
  - paraneoplastic myelopathy
  - diseases causing pain over certain body segments (e.g. cholecystitis, pyelonephritis, intestinal pathology). To differentiate from these, look for dermatomal distribution, increase with Valsalva maneuver, and accompanying sensory and/or motor changes in LEs which suggest cord/radicular lesion. Radiographic studies are frequently required to differentiate
  - diseases of vertebral structures (e.g. Paget's disease, giant cell tumors of bone (*see page 742*), etc.)

21.12.1.2. Specific intramedullary spinal cord tumors

Ependymoma

Key concepts:

> - the most common glioma of lower cord, conus and filum (most ependymomas in conus and filum are *myxopapillary* ependymomas). More common in adults
> - evaluation: includes imaging the entire neuraxis (usually with enhanced MRI: cervical, thoracic, lumbar & brain) because of potential for seeding through CSF
> - associated cysts are common
> - treatment: surgical excision (most are encapsulated)

The most common glioma of the lower spinal cord, conus and filum (see *Myxopapillary ependymoma* below). Slow-growing. Benign. Slight male predominance; slight peak in 3rd to 6th decade. Over 50% in filum, next most common location is cervical. Histologically: papillary, cellular, epithelial, or mixed (in filum, myxopapillary ependymoma is most common, *see below*). Cystic degeneration in 46%. May expand spinal canal in filum[734]. Usually encapsulated and minimally vascular (papillary: may be highly vascular; may

cause SAH). Symptoms present > 1 yr prior to diagnosis in 82% of cases[512].

Myxopapillary ependymoma

Ependymomas of the conus medullaris and the filum terminale are usually of the myxopapillary subtype. WHO grade I. Usually solitary. Histology: papillary, with microcystic vacuoles, mucosubstance; connective tissue. No anaplasia, but CSF dissemination occurs rarely (can seed intracranially following removal of spinal tumor[735]). Denovo intracranial lesions also occur rarely. Rare reports of systemic mets[714]. Outside the CNS, may occur in sacrococcygeal subcutaneous tissues from heterotopic rests of ependymal cells[736].

Surgical removal of filum tumors consists of coagulating and dividing the filum terminale just above and below the lesion (see *Distinguishing features of the filum terminale intraoperatively*, page 255), and excising it in total. The filum is first cut above the lesion to prevent retraction upwards.

Astrocytoma

Uncommon in first year. Peak: 3rd - 5th decade. Male:female = 1.5:1. The ratio of low-grade:high-grade = 3:1 in all ages[734]. Occurs at all levels, thoracic most common, then cervical. 38% are cystic; cyst fluid usually has high protein.

Dermoid and epidermoid

Epidermoids are rare before late childhood. Slight female predominance. Cervical and upper thoracic rare; conus common. Usually ID-EM, but conus/cauda equina may have IM component (completely IM lesions rare).

Lipoma

May occur in conjunction with spinal dysraphism (see *Lipomyeloschisis*, page 251). The following considers lipomas that occur in the absence of spinal dysraphism.

Peak occurrence: 2nd, 3rd and 5th decade. Technically hamartomas. No sex predominance. Usually ID-EM (a sub-type is truly IM and essentially replaces the cord[737]), cervicothoracic region is the most common location. NB: unlike other IMSCT's, most common symptom is ascending mono- or para-paresis (c.f. pain). Sphincter disturbance is common with low lesions. Local subcutaneous masses or dimples are frequent. Malis recommends early subtotal removal at about 1 year age in asymptomatic patient[737]. Superficial extrasacral removal is inadequate, as patients then develop dense scarring intraspinally leading to fairly

rapid severe neurological damage with poor salvageability even after the definitive procedure.

HEMANGIOBLASTOMA

Usually non-infiltrating, well demarcated, may have cystic caps. 33% of patients with spinal hemangioblastoma will have von Hippel-Lindau disease (*see page 667*). Cannot incise nor core because of vascularity. Requires microsurgical approach similar to AVM, possibly with intraoperative hypotension.

METASTASES

Most spinal mets are extradural, only a few hundred case reports of IMSCT mets exist[738], accounting for 3.4% of symptomatic metastatic spinal cord lesions[739]. Primaries include: small-cell lung Ca[740], breast Ca, malignant melanoma, lymphoma and colon Ca[739, 741]. Ca rarely presents first as an intramedullary spinal met.

PRESENTATION

1. pain: the most common complaint. Almost always present in filum tumors (exception: lipomas)[729]. Possible pain patterns:
   - radicular: increases with Valsalva maneuver and spine movement. Suspect SCT if dermatome is unusual for disk herniation
   - local: stiff neck or back, Valsalva maneuver increases. ★ Pain during recumbency ("nocturnal pain") is classic for SCT
   - medullary (as in syrinx): oppressive, burning, dysesthetic, non-radicular, often bilateral, unaffected by Valsalva maneuver
2. motor disturbances
   - weakness is 2nd or 3rd most common complaint. Usually follows sensory symptoms temporally
   - children present most frequently with gait disturbances
   - syringomyelic syndrome: suggests IMSCT. Findings: UE segmental weakness, decreased DTR, dissociative anesthesia (*see below*)
   - long-tract involvement → clumsiness and ataxia (distinct from weakness)
   - atrophy, muscle twitches, fasciculations
3. non-painful sensory disturbances
   - dissociated sensory loss: decreased pain and temperature, preserved light touch (as in Brown-Séquard syndrome, *see page 950*). There is

disagreement whether this is common[715] or uncommon[742] in IMSCT. ± non-radicular dysesthesias (early), with upward extension[743]
  - paresthesias: either radicular or “medullary” distribution
4. sphincter disturbances
   - usually urogenital (anal less common) → difficulty evacuating, retention, incontinence, and impotence. Early in conus/cauda equina lesions, especially lipomas (pain not prominent)
   - sphincter dysfunction common in age < 1 yr due to frequency of lumbosacral lesions (dermoids, epidermoids, etc.)
5. miscellaneous symptoms:
   - scoliosis or torticollis
   - SAH
   - visible mass over spine

TIME COURSE OF SYMPTOMS

Onset usually insidious, but abruptness occurs (benign lesions in children occasionally progress in hours). The onset is often erroneously attributed to coincidental injury. Temporal progression[A] has been divided into 4 stages[744]:

1. pain only (neuralgic)
2. Brown-Séquard syndrome
3. incomplete transectional dysfunction
4. complete transectional dysfunction

A. 78% (of 23) ependymomas, 74% (of 42) gliomas, all 7 dermoids, and 50% (of 8) lipomas reached latter 2 stages before diagnosis (not affected by location in cross-sectional nor longitudinal dimension of SC (excludes conus lesions - more frequently diagnosed in 1st stage) (a pre-CT study)

DIAGNOSIS

It is usually difficult to distinguish IMSCT, ID-EM and ED on clinical grounds[715]. Schwannomas often start with radicular symptoms that later progress to cord involvement. Most IMSCTs are located posteriorly in cord which may cause sensory findings to predominate early[728].

DIAGNOSTIC STUDIES

Plain radiographs: vertebral body destruction, enlarged intervertebral foramina, or increases in interpedicular distances suggests ED SCT.

Lumbar puncture: Elevated protein is the most common abnormality[714] seen in ≈ 95%. The reported range with primary IMSCT's is 50-2,240 mg%. Glucose is normal except with meningeal tumor. SCT can cause complete block, indicated by:

- **Froin's syndrome**: clotting (due to fibrinogen) and xanthochromia of CSF
- **Queckenstedt's test** (failure of jugular vein compression to increase CSF pressure, which it normally does in the absence of block)
- barrier to flow of myelographic contrast media

MRI: mainstay of diagnosis. Ependymomas enhance intensely and are often associated with hemorrhage and cysts. Cord edema may mimic a cyst.

Myelography: classically shows fusiform cord widening (may be normal early). Distinct from ED tumors which produce hourglass deformity (with incomplete block) or paintbrush effect (with complete block), or ID-EM tumors which produce a capping effect with a sharp cutoff (meniscus sign) (*see page 746*).

CT: some IMSCTs enhance with IV contrast. Metrizamide CT distinguishes IMSCT from ID-EM (poor in differentiating IMSCT subtypes).

Spinal angiography: rarely indicated, except in hemangioblastoma (may be suspected on myelography or MRI by linear serpiginous structures). MRI may obviate this test.

MANAGEMENT

Surgery should be performed as soon as possible (generally not as an emergency) after diagnosis since surgical results correlate with the preoperative neurologic condition, and it makes no sense to follow the patient as they develop progressive neurologic deficit[745] (some of which may be irreversible).

Astrocytomas: For low grade lesions, if a plane can be developed between the tumor and spinal cord (when it can, it usually consists of a thin gliotic layer traversed by small blood vessels and adhesions[728]), an attempt at total excision is an option[746]. For high grade astrocytomas or for low-grade astrocytomas without a plane of separation, biopsy alone or biopsy plus limited excision is recommended[746].

For high-grade lesions, post-op RTX (± chemotherapy) is recommended[746]. RTX is not supported following radical resection of low grade gliomas[746].

Ependymomas: An attempt at gross total removal should be attempted. XRT is not recommended following gross total removal[746].

TECHNICAL SURGICAL CONSIDERATIONS

- position: usually prone, well padded & securely taped to avoid movement if MEP monitoring is to be used. Other options include: lateral oblique, sitting
- if a cystic component is suspected, partial aspiration with a 25 Ga needle once the spinal cord is exposed will decrease the pressure (avoid total aspiration which makes it more difficult to locate the tumor)[747]. If the cyst forms a "cap" at either end of the tumor, the dura does not need to be opened over the cyst as drainage can be accomplished with removal of tumor
  - adjunctive options include:
    - intraoperative spinal cord monitoring (SSEP, and motor evoked potentials **(MEPs)**[748]): SEPs almost always degrade with the initial myelotomy and do not correlate well with motor outcome[749] (which is critical)[750, 751] (e.g. it is not unusual for SEPs to be lost during the initial myelotomy without correlation with outcome) and postoperative motor deficit may occur in spite of unaltered intraoperative SEPs[748, 749] and conversely SEPs may be lost without motor deficit. However, proof of improved outcomes with MEP monitoring is also lacking[750]
    - intraoperative ultrasound: also controversial[751], favored by some experts. Astrocytomas are usually isoechoic with spinal cord, whereas ependymomas are usually hyperechoic
  - a myelotomy is performed either in the midline or just to one side of the dorsal midline to avoid the posteromedian vein. Alternatively, if the tumor is known to be very superficial off the midline (which may be confirmed by ultrasound), entry may be made there. Tumors may cause distortion and displacement of the midline - look for dorsal root entry zones on both sides to identify the midline as the mid-point between root entry zones
  - 6-0 silk sutures are placed through the pial edge to gently retract the spinal cord open. Standard sized (i.e. non-micro) bayonet forceps can be used to gently spread tissues
  - copious irrigation is used whenever bipolar cautery is employed on the tumor/spinal cord, to minimize transference of heat to the spinal cord. Monopolar cautery should not be used[747]
  - either laser or ultrasonic aspiration (USA) are used to debulk tumor from within until the glial-tumor interface is reached. Charring from laser may make it more difficult to recognize the glial/tumor interface than USA, and the laser tends to be slower when debulking larger tumors
  - watertight closure is critical

Table 21-80 Key concepts in surgical removal of IMSCT

• in almost all cases, IMSCTs should be debulked from within (to avoid manipulation of neural tissue) with ultrasonic aspirator or laser, and no attempt should be made initially to develop a plane between tumor and spinal cord (even for ependymomas, which of the 3 most common IMSCTs is the only one that actually has such a plane)
• if MEPs are monitored: although it is arbitrary, it is suggested that tumor removal should be discontinued if the amplitudes drop to ≤ 50% of baseline

PROGNOSIS

No well designed studies give long term functional results with microsurgery, laser and radiotherapy. Better results occur with lesser initial deficits[728]. Recurrence depends on totality of removal, and on growth pattern of the specific tumor.

Ependymoma: total extirpation improves functional outcome, and myxopapillary ependymomas fare better than the "classic" type[512]. Best functional outcome occurs with modest initial deficits, symptoms < 2 years duration[752], and total removal. Survival is independent of extent of excision.

Astrocytomas: radical removal rarely possible (cleavage plane unusual even with microscope). Long term functional results poorer than ependymomas. There is 50% recurrence rate in 4-5 yrs.

21.12.2. Spinal schwannomas

Key concepts:

- slow growing benign tumors
- most (75%) arise from the dorsal (sensory) rootlets
- early symptoms are often radicular
- recurrence is rare after total excision (except in neurofibromatosis)

Incidence: 0.3-0.4/100,000/yr. Most occur sporadically and are solitary, but they may also be associated with neurofibromatosis (*see page 722*) primarily type 2 (NF2), but can occur with type 1.

Configurations

Most are entirely intradural, but 8-32% may be completely extradural[753, 754], 1-19% are a combination, 6-23% are dumbbell, and 1% are intramedullary.

Dumbbell tumors. Definition: tumors that develop an “hourglass” shape as a result of an anatomic barrier encountered during growth. Not all dumbbell tumors are Schwannomas (e.g. neuroblastoma, *see page 748*). Most have a contiguous intraspinal, foraminal (usually narrower) and extraforaminal components (widening of the neural foramen is a characteristic finding, can be recognized even on plain films, and speaks to the longstanding benign nature of the lesion). The waist may also be due to a dural constriction.

Asazuma et al.[755] classification system for dumbbell spinal Schwannomas is shown in *Figure 21-5*.

Type I tumors are intradural and extradural and are restricted to the spinal canal. The constriction occurs at the dura.

Type II are all extradural, and are subclassified as: IIa do not extend beyond the neural foramen, IIb = inside spinal canal + paravertebral, IIc = foraminal + paravertebral.

Type IIIa are intradural and extradural foraminal, IIIb are intradural and extradural paravertebral.

Type IV are extradural and intravertebral. Type V are extradural and extralaminar with laminar invasion. Type VI show multidirectional bone erosion.

Craniocaudal spread: IF & TF designate the number of intervertebral foramina and transverse foramina involved, respectively (e.g. IF stage 2 = 2 foramens).

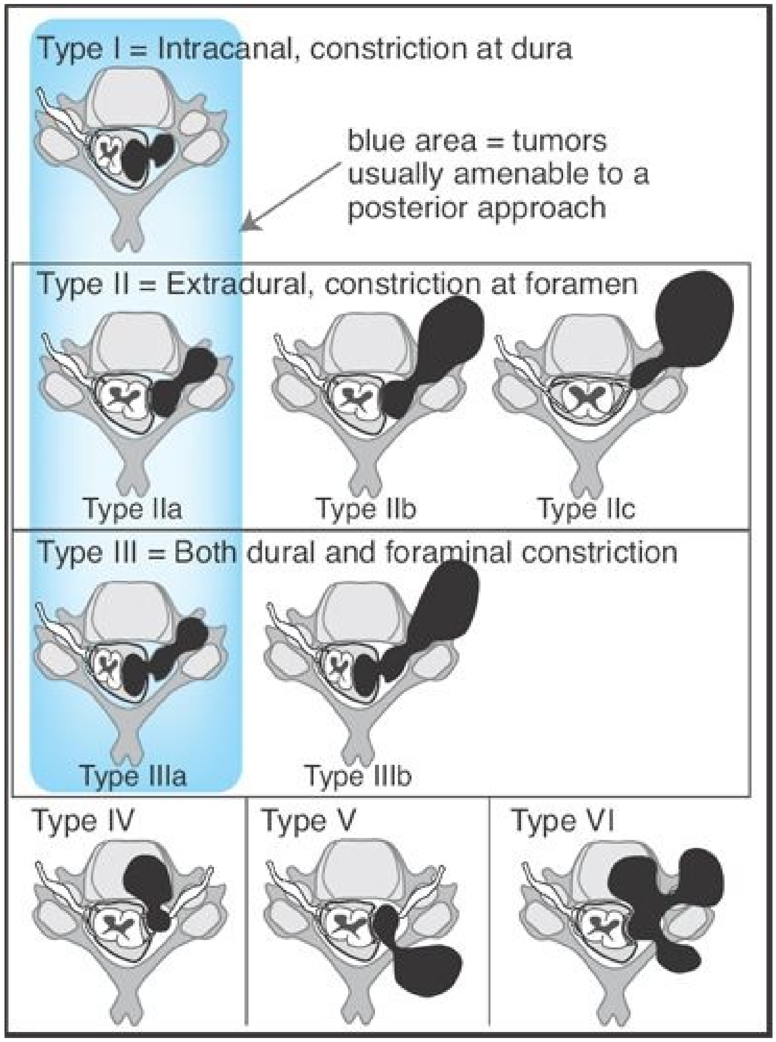

Figure 21-5 Classification of dumbbell spinal tumors Modified with permission from Asazuma T, Yoshiaki T, Hirofumi M, et al.: Surgical strategy for cervical dumbbell tumors based on a three-dimensional classification. **Spine** 29 (1): E10-4, 2003

Schwannomas involving C1 & C2: May involve vertebral arteries and require additional caution.

Clinical

Patients typically present with local pain. Neurologic deficits develop late.

Pathology

Composed of Antoni A (compact, interwoven bundles of long, spindly Schwann cells) and Antoni B tissue (sparse areas of Schwann cells in a loose eosinophilic matrix).

Treatment

Posterior approaches: Types I, IIa IIIa, some upper cervical IIIb and some VI are generally amenable to a posterior approach. IIa & IIIa usually require total facetectomy for complete removal[755]. Reconstruction with instrumentation may be needed if substantial posterior disruption occurs.

Anterior and combined anterior/posterior approaches: Asazuma et al.[755] recommend a combined approach for Type IIb, IIc and IIIb lesions where the extraforaminal extension is large (viz. beyond the vertebral arteries). Reconstruction with instrumentation was required for some tumors (≈ 10% of all patients treated) which were type IV (2 patients), IIIb (1 pt) and VI (1 pt).

Nerve sacrifice: It is usually possible to preserve some fascicles of the nerve root, although sometimes section of the entire nerve root is required. New deficits may not occur since involved fascicles are often nonfunctional, and adjacent roots may compensate. The risk for motor deficit is higher for schwannomas than for neurofibromas, for cervical vs. lumbar tumors, and for cervical tumors with extradural extension.

Outcome

Recurrence is rare following gross total excision, except in the setting of NF2.

21.12.3. Bone tumors of the spine

For tumors that can affect the spine but are not necessarily of the spine, *see page 728*.

1. metastatic: the most common malignancy of spine
   A. common osteolytic metastatic tumors include (*see page 742*):
      1. lung
      2. breast
      3. prostate
      4. lymphoma: most cases represent spread of systemic disease (secondary lymphoma), however some may be primary (*see page 730*)
      5. plasmacytoma: *see page 740*
      6. multiple myeloma: *see page 740*

        7. eosinophilic granuloma: *see page 729* for differentiating features
    B. metastases that may be osteoblastic:
        1. in men: prostate Ca is the most common
        2. in women: breast Ca is the most common
    C. Ewing's sarcoma: *see page 729*
    D. chloroma: focal infiltration of leukemic cells
2. primary spinal tumors (very rare)
    A. benign
        1. vertebral hemangioma: *see page 738*
        2. osteoid osteoma: *see page 736*
        3. osteoblastoma: *see page 736*
        4. aneurysmal bone cyst: cavity of highly vascular honeycomb surrounded by a thin cortical shell which may expand (*see page 728*)
        5. osteochondroma (chondroma): *see page 728*
        6. giant cell tumors of bone: AKA osteoclastoma (*see page 742*). Almost always benign with pseudomalignant behavior
    B. malignant
        1. chondrosarcoma: *see page 728*
        2. chordomas: *see page 675*
        3. osteogenic sarcoma: rare in spine

21.12.3.1. Osteoid osteoma and osteoblastoma

Key concepts:

> - both are benign bone tumors
> - histologically identical, differentiation depends on size (≤1 cm = osteoid osteoma, > 1 cm = osteoblastoma)
> - can occur in the spine and may cause neurologic symptoms (esp. osteoblastoma)
> - high cure rate with complete excision

Two types of benign osteoblastic lesions of bone: osteoid osteoma **(OO)** and benign osteoblastoma **(BOB)** (*see Table 21-81*). They are indistinguishable histologically, and must be differentiated based on size and behavior.

Characteristically cause night pain and pain relieved by aspirin (see *Clinical* below).

Osteoblastoma is a rare, benign, locally recurrent tumor with a predilection for spine, that may rarely undergo sarcomatous change (to osteosarcoma[757], only a handful of known cases of this). More vascular than OO[758].

Differential diagnosis (for lesions with similar symptoms and increased uptake on radionuclide bone scan):

1. benign osteoblastoma
2. osteoid osteoma: more pronounced sclerosis of adjacent bone than BOB
3. osteogenic sarcoma: rare in spine
4. aneurysmal bone cyst: typically trabeculae in central, lucent region (*see* *page 728*)
5. unilateral pedicle/laminar necrosis

Table 21-81 Comparison of osteoid osteoma and benign osteoblastoma[756]

	Osteoid osteoma	**Benign osteoblastoma**
percent of primary bone tumors	3.2%	
percent of primary vertebral tumors	1.4%	
percent that occur in spine	10%	35%
size limitations	≤ 1 cm	> 1 cm
growth pattern	confined, self limiting	more extensive, may extend into spinal canal
potential for malignant change?	no	rare
location within spine (83 patients)		
% in cervical spine	27%	25%
% in thoracic spine		35%
% in lumbar region	59%	35%
location within vertebra (81 patients)		
lamina only	33%	16%
pedicle only	15%	32%
articular facet only	19%	0
vertebral body **(VB)** only	7%	5%
transverse process only	6%	8%
spinous process	5%	5%
> 1 element of neural arch	6%	19%

combined posterior elements & VB	0	11%

CLINICAL

See Table 21-82 for signs and symptoms. Tenderness confined to vicinity of the lesion occurs in ≈ 60%. 28% of patients with BOB presented with myelopathy. OO presented with neurologic deficit in only 22%.

EVALUATION

Bone scans are a very sensitive means for detecting these lesions. Once localized, CT or MRI may better define the lesion in that region.

Caution re needle biopsy: if the lesion turns out to be osteosarcoma, the contaminated needle tract can result in worse prognosis.

Osteoid osteoma

Radiolucent area with or without surrounding density, often isolated to pedicle or facet. May not show up on tomograms.

Osteoblastoma

Most are expansile, destructive lesions, with 17% having moderate sclerosis. 31% have areas of ↑ density, 20% surrounded by calcified shell. Often a contralateral spondylolysis[757].

Table 21-82 Signs and symptoms in 82 patients[756]

Finding	Osteoid osteoma	Benign osteoblastoma
pain on presentation	100%	100%
pain increased by motion	49%	74%
pain increased by Valsalva	17%	36%
nocturnal pain	46%	36%
pain relieved by aspirin	40%	25%
radicular pain	50%	44%
scoliosis	66%	36%
neurologic abnormalities	22%	54%
myelopathy	0	28%

weakness	12%	51%
atrophy	9%	15%

Treatment

In order to obtain a cure, these lesions must be completely excised. The role of radiation therapy is poorly defined in these lesions, but is probably ineffective[757].

Osteoid osteoma

Cortical bone may be hardened and thickened, with granulomatous mass in underlying cavity.

Osteoblastoma

Hemorrhagic, friable, red to purple mass well circumscribed from adjacent bone. Complete excision → complete pain relief in 93%. Curettage only → pain relief, with more likely recurrence. Recurrence rate with total excision is ≈ 10%.

21.12.3.2. Osteosarcoma

The most common primary bone cancer. More common in children, usually occurring near the ends of long bones, but also in the mandible, pelvis, and rarely in the spine[759]. Spinal osteosarcoma usually occurs in the lumbosacral region in males in their 40's, sometimes arising from ares of osteoblastoma or Paget's disease. If a percutaneous biopsy reveals osteosarcoma, the contaminated needle tract can increase the difficulty of subsequent surgery. Poor prognosis, median survival = 10 months[759].

21.12.3.3. Vertebral hemangioma

Key concepts:

- the most common primary spine tumor. Benign
- rarely symptomatic (< 1.2%), symptoms more commonly from compression fracture, disc herniation, and rarely neural compression from bone expansion…
- MRI: small lesions are hyperintense on T1WI and T2WI. Larger ones may be hypointense. X-ray: striations (corduroy pattern) or "honeycomb"

appearance. Bone scan: usually do not have increased uptake

- treatment: incidental lesions require no routine follow-up. Biopsy when mets are a strong consideration. Treatment options (when indicated): XRT, embolization, vertebroplasty (better than kyphoplasty), surgery

Vertebral hemangiomas **(VH)**, AKA spinal hemangioma, cavernous hemangioma, or hemangiomatous angioma. Benign lesions of the spine. The most common primary tumor of the spine (10-12% of primary spinal bone tumors). Estimated incidence: 9-12%[760, 761]. 70% are solitary, 30% are multiple (up to 5 levels may be involved, often noncontiguous). Lumbar and lower thoracic spine are the most common locations, cervical and sacral lesions are rare. Lesions involve only the vertebral bodies in ≈ 25%, posterior spinal arch in ≈ 25%, and both areas in ≈ 50%. Occasional cases of purely extradural lesions have been described[762]. Intramedullary lesions are even less common[763]. Typically found in post-pubertal females.

Malignant degeneration has <u>never</u> been reported. Mature thin-walled blood vessels of varying sizes replace normal marrow, producing hypertrophic sclerotic bony trabeculations oriented in a rostral-caudal direction in one of two forms: cavernous (venous) or capillary (difference in subtype carries no prognostic significance).

Presentation

1. incidental: most VH are asymptomatic, these require no follow-up (*see below*)
2. symptomatic: only 0.9-1.2% are symptomatic. There may be a hormonal influence (unproven) that may cause symptoms to increase with pregnancy (could also be due to increased blood volume and/or venous pressure)[764] or to vary with the menstrual cycle and may explain why symptoms rarely occur before puberty
   A. pain: occasionally VH may present with pain localized to the level of involvement with no radiculopathy. However, pain is more often due to other pathology (compression fracture, herniated disc, spinal stenosis…) rather than the VH itself
   B. progressive neurologic deficit: this occurs rarely, and usually takes the form of thoracic myelopathy. Deficit may be caused by the following mechanisms
      1. subperiosteal (epidural) growth of tumor into the spinal canal
      2. expansion of the bone (cortical "blistering") with widening of the

pedicles and lamina producing a “bony” spinal stenosis
3. compression by vessels feeding or draining the lesion
4. compression fracture of the involved vertebra (very rare)[765]
5. spontaneous hemorrhage → spinal epidural hematoma[766] (rare)
6. spinal cord ischemia due to “steal”

EVALUATION

Plain x-rays: classically show coarse vertically oriented striations (corduroy pattern) or a “honeycomb” appearance. At least ≈ one third of the VB must be involved to produce these findings on plain x-ray (*see Figure 21-6*).

Bone scan: VH are usually not hot (unless a compression fracture has occurred), which may help distinguish VH from metastatic disease (which usually light up).

CT: diagnostic procedure of choice. “**Polka-dot sign**”[817]: multiple high density dots represents cross-sections through thickened trabeculae (*see Figure 21-7*).

MRI: small hemangiomas are focal, round, and hyperintense on T1WI and T2WI. More extensive lesions can be hypointense. Lesions that tend not to evolve (mottled increased signal on T1WI and T2WI, possibly due to adipose tissue) differ from those that tend to be symptomatic (isointense on T1WI,hyperintense on T2WI).

Spinal angiography: also may help distinguish nonevolutive (normal or slight increased vascularity compared to adjacent bone) from symptomatic (moderate to marked hypervascularity) lesions. Therapeutic: if the feeding artery does not also supply the anterior spinal artery, it may be embolized preoperatively or sacrificed at surgery.

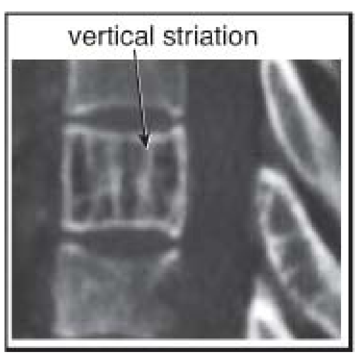

Figure 21-6 Vertebral hemangioma. Sagittal CT reconstruction

Figure 21-7 Vertebral hemangioma. Axial CT showing polka dot sign

Treatment[760]

1. asymptomatic VH require no routine follow-up or evaluation unless pain or neurologic deficit develop, which are rare occurrences in incidentally discovered VH
2. biopsy: may be indicated in cases where diagnosis is uncertain (e.g. when metastases are a strong consideration). In spite of highly vascular nature, there have been no reported bleeding complications with CT guided biopsy
3. those presenting with pain or neurologic deficit
   A. radiation therapy: may be used alone for painful lesions, preoperatively as a surgical adjunct, or post-op following incomplete removal. VH are radiosensitive and undergo sclerotic obliteration. Total dosage should be ≤ 40 Gy to reduce risk of radiation myelopathy. Improvement in pain may take months to years, and no radiographic evidence of response may occur
   B. embolization: provides more rapid relief of pain than RTX, can also be used pre-op as surgical adjunct. Risks spinal cord infarction if major radicular artery (e.g. artery of Adamkiewicz, *see page 96*) is embolized
   C. vertebroplasty: (*see page 994*) may be better than kyphoplasty for VH because kyphoplasty destroys the trabecular bone
   D. surgery: for painful lesions that fail to respond to above measures, or for lesions with progressive neurologic deficit (*see below*)

Surgical treatment

For indications, *see above*. Recommended management is shown in *Table 21-83*.

Table 21-83 Recommendations for surgical management of VH*[760]

VH involvement	Approach	Post-op RTX?
posterior elements only	radical excision via posterior approach	not for total excision
VB involvement with anterior canal compression (with or without ST in canal)	anterior corpectomy with strut graft	
VB involved but no expansion, ST in lateral canal	laminectomy with removal of soft-tissue	follow serial CT, give RTX if VB expansion or ST expansion
extensive involvement of anterior and posterior vertebral elements with circumferential bone expansion, no ST compression	laminectomy	either RTX, or close follow-up with CT and RTX for ST recurrence or progressive VB expansion
extensive anterior and posterior involvement with ST in anterior canal	anterior corpectomy with strut graft	

* abbreviations: VB = vertebral body, ST = soft-tissue component of VH, RTX = radiation treatment

Major risks of surgery: blood loss, destabilization of the spine, neurologic deficit (during surgery, or post-op usually from epidural hematoma). Recurrence rate is 20-30% after subtotal resection, usually within 2 yrs. Patients with subtotal resection should have RTX which lowers recurrence rate to ≈ 7%.

21.12.3.4. Multiple myeloma

Multiple myeloma **(MM)** (or simply [*myeloma*) is a neoplasm of a single clone of plasma cells characterized by proliferation of plasma cells in bone marrow, infiltration of adjacent tissues with mature and immature plasma cells, and the production of an immunoglobulin, usually monoclonal IgG or IgA (referred to collectively as M-protein[767]). Circulating pre-myeloma cells lodge in appropriate microenvironments (e.g. in bone marrow) where they differentiate and expand. Although MM is often referred to in the context of "metastatic lesions" to bone, it is also sometimes considered a primary bone tumor. If only a single lesion is identified, then it is referred to as a plasmacytoma (*see below*).

MM presents as a result of the following (underscored items are characteristic for MM):

1. proliferation of plasma cells: interferes with normal immune system function → increased <u>susceptibility to infection</u>
2. bone involvement
   A. bone marrow involvement → destruction of hematopoietic capacity → normocytic normochromic <u>anemia</u>, leukopenia, thrombocytopenia
   B. bone resorption
      1. → weakening of the bone → <u>pathologic fractures</u> (*see below*)
      2. → <u>hypercalcemia</u> (present initially in 25% of MM patients, *see below*)
   C. swelling or local tenderness of bone
   D. <u>bone pain</u>: characteristically induced by movement, and absent at rest
   E. spinal involvement
      1. invasion of spinal canal in ≈ 10% of cases → spinal cord compression → myelopathy (*see page 742*)
      2. nerve root compression (radiculopathy)
3. overproduction of certain proteins by plasma cells. May lead to:
   A. hyperviscosity syndrome
   B. cryoglobulinemia
   C. amyloidosis
   D. <u>renal failure</u>: multifactorial, but monoclonal light chains play a role

Skeletal disease

MM involvement is by definition multiple, and is usually restricted to sites of red marrow: ribs, sternum, spine, clavicles, skull, or proximal extremities. Lesions of the spine and/or skull are the usual reasons for presentation to the neurosurgeon.

Bone resorption in MM is not due simply to mechanical erosion by plasma cells. Increased osteoclastic activity has been observed.

Plasma cell tumors of the skull involving the cranial vault usually do not produce neurologic symptoms. Cranial nerve palsies can arise from skull base involvement. Orbital involvement may produce proptosis (exophthalmos).

Neurologic involvement

Neurologic manifestations can occur as a result of:

1. tumor involvement of bone causing compression (*see above*)
   A. tumor in spine with compression of spinal cord or nerve roots

B. tumor in skull with compression of brain or cranial nerves

2. deposition of amyloid within the flexor retinaculum of the wrist → carpal tunnel syndrome (the median nerve itself does not contain amyloid, and therefore responds well to surgical division of the transverse carpal ligament, *see page 811*)
3. diffuse progressive sensorimotor polyneuropathy: occurs in 3-5% of patients with MM (also, *see page 799*)
   A. about half are due to amyloidosis (*see page 800*)
   B. polyneuropathy can also occur without amyloidosis, especially in the rare osteosclerotic variant of MM
4. multifocal leukoencephalopathy has been described in MM[769]
5. hypercalcemia: may produce a dramatic encephalopathy with confusion, delerium or coma. Neurologic symptoms of hypercalcemia associated with MM are more common than in hypercalcemia of other etiologies
6. very rare: intraparenchymal metastases[770]

Epidemiology

Incidence in the U.S.: ≈ 1-2 per 100,000 in caucasians, and is ≈ twice that in blacks. MM accounts for 1% of malignancies, and 10% of hematologic cancers. Peak age of occurrence: 60-70 yrs of age, with < 2% of patients being < 40 yrs old. Slightly more common in males. Monoclonal gammopathy without MM occurs in ≈ 0.15% of the population, and in long-term follow-up 16% of these develop MM with an annual rate of 0.18%[768].

Evaluation

Diagnostic criteria for MM is shown in *Table 21-84*. Tests for MM include:

1. 24 hour urine for kappa Bence-Jones protein[A] present in 75%
2. bloodwork: serum protein electrophoresis **(SPEP)** and immune electrophoresis **(IEP)** (looking for IgG kappa band)[A]
3. skeletal radiologic survey. Characteristic x-ray finding: multiple, round, “punched-out” (sharply demarcated) lytic lesions in the bones typically involved (*see above*). Osteosclerotic lesions are seen in < 3% of patients with MM. Diffuse osteoporosis may also be seen
4. CBC: anemia eventually develops in most patients with MM. It is usually of moderate severity (Hgb ≈ 7-10 gm%) with a low reticulocyte count
5. technetium-99m nuclear bone scan is usually negative in untreated MM (due to rarity of spontaneous new bone formation) and is less sensitive

than conventional radiographs. Therefore it is not usually helpful except perhaps to implicate etiologies *other* than MM to explain the observed findings. After treatment, bone scan may become positive as osteoblastic activity ensues (“flare” response)

6. serum creatinine: for prognostication
7. bone marrow biopsy: virtually all MM patients have “myeloma cells” (although sensitive, this is not specific and other diagnostic criteria should be sought)

A. monoclonal proteins cannot be detected in the urine or serum of ≈ 1% of MM patients. Two or more monoclonal bands are produced in ≈0.5-2.5% of patients with MM[772]

Table 21-84 Criteria for diagnosis of MM*

1. cytologic criteria A. marrow morphology: plasma cells and/or myeloma cells ≥ 10% of 1000 or more cells B. biopsy proven plasmacytoma
2. clinical and laboratory criteria A. myeloma protein (M-component) in serum (usually > 3 gm/dl) or urine IEP B. osteolytic lesions on x-ray (generalized osteoporosis qualifies if marrow contains > 30% plasma or myeloma cells) C. myeloma cells in ≥ 2 peripheral blood smears

* diagnosis requires[771]: 1 A & B, or 1A or 1B and 2A, 2B, or 2C

Treatment

Many aspects of treatment fall into the purvey of the oncologist (*see review*[768]). Some aspects pertinent to neurosurgical care include:

1. XRT: MM Is very radiosensitive. Focal XRT for pain due to readily identifiable bone lesions, may allow pathologic fractures to heal and is effective in spinal cord compression (*see page 708*)
2. mobilization: immobilization due to pain and fear of pathologic compression fractures leads to further detrimental increases in serum calcium and weakness
3. pain control: mild pain often responds well to salicylates (contraindicated in thrombocytopenia). Local XRT is also effective (*see below*)
4. percutaneous kyphoplasty (*see page 994*) may be used for some spine lesions
5. therapy for hypercalcemia usually improves symptoms related to that
6. bisphosphonates inhibit bone resorption and rapidly reduces

hypercalcemia (*see page 500*). Pamidronate is currently preferred over older agents
7. bortezomib (Velcade®): proteasome inhibitor, for treatment of refractory MM

Prognosis

Untreated MM has a 6 month median survival. Solitary plasmacytoma has a 50% 10-year survival. If there is an solitary site of involvement but M-protein is present (i.e. essentially a plasmacytoma except for the M-protein), elimination of the M-protein following XRT indicates a 50-60% chance of remaining free of MM, if the M-protein doesn't resolve, there is a high chance of developing MM.

Plasmacytoma

A neoplasm of a single clone of plasma cells similar to multiple myeloma (*see above*) but meeting the following criteria:

1. there must be no other lesions on complete skeletal survey (not bone scan)
2. bone marrow aspirate must show no evidence of myeloma
3. and serum and urine electrophoresis should show no M-protein

MM will develop in 55-60% of patients with a solitary plasmacytoma in 5 years, and in 70-80% by 10 yrs.

Treatment

1. local XRT provides good local control rates
2. percutaneous kyphoplasty (*see page 994*)

21.12.3.5. Giant cell tumors of bone

AKA osteoclastoma (cells arise from osteoclasts). In the same general category as aneurysmal bone cysts. Typically arise in adolescence. Most common in knees and wrists. May be seen by a neurosurgeon when they arise in the skull (especially the skull base, and in particular the sphenoid bone), or in the vertebral column (≈ 4% occur in sacrum).

Pathology

Lytic with bony collapse. Almost always benign with pseudomalignant behavior (recurrence is common, and pulmonary mets can occur).

Evaluation

Work-up includes chest CT because of possibility of pulmonary mets.

Treatment

Intratumoral curettage, possibly aided by pre-op embolization. Recurrence rate with this treatment (even if resection is subtotal) is only ≈ 20%. Role of RTX is controversial[719] because of the possibility of malignant degeneration (therefore use RTX only for non-resectable recurrence). Use of osteoclast inhibiting drugs (bisphosphonates e.g. pamidronate, *see page 501*) has met with some success following subtotal resection.

For gross residual disease after resection, re-resection is a consideration.

Cryosurgery with liquid nitrogen has been employed in long bones. Its use is limited in neurosurgical cases because of risk of injury to adjacent neural structures (brain, spinal cord) and cryotherapy induced fractures, although it has been described for use in the sacrum[773].

Close follow-up is required due to propensity for recurrence. MRI or CT initially q 3 months is suggested.

21.12.4. Spinal epidural metastases

Key concepts:

- suspected in a cancer patient with back pain that persists in recumbency
- occurs in ≈ 10% of all cancer patients
- 80% of primary sites: lung, breast, GI, prostate, melanoma and lymphoma
- many treatments reduce pain. Surgery + XRT in selected cases increases chances of preserving ambulation & produces a modest improvement in survival
- if no neurologic compromise or bony instability, usual treatment: biopsy (CT- or fluoro-guided) followed by XRT (surgical indications: *Table 21-88*, page 745)
- surgery not helpful for: *total* paralysis > 8 hrs, loss of ambulation > 24 hrs, and not recommended for prognosis < 3-4 months survival, poor medical condition (poor PFTs…), or radiosensitive tumor

Spinal epidural metastases **(SEM)** occur in up to 10% of cancer patients at some time[774], and are the most common spinal tumor. 5-10% of malignancies

present initially with cord compression[775]. For other etiologies of spinal cord compression, see items marked with a dagger (†) under *Myelopathy* on page 1185.

Routes of metastasis to spine:

1. arterial
2. venous: via spinal epidural veins (**Batson's plexus**[776])
3. perinervous (direct spread)

The usual route of spread is hematogenous dissemination to the VB with erosion back through pedicles and subsequent extension into the epidural space (i.e. anterior epicenter). Less commonly may initially metastasize to lateral or posterior aspect of canal. Most metastases (mets) are epidural, only 2-4% are intradural, and only 1-2% are intramedullary. Distribution between cervical, thoracic and lumbar spine is proportional to the length of the segment, thus the thoracic spine is the most common site (50-60%).

Primary sources of spine mets

Table 21-85 shows primary tumor types that give rise to SEM. The majority are common primaries that tend to metastasize to bone (lung, breast, prostate, renal-cell and thyroid). Rare tumors that may go to bone include the myxoid subtype of liposarcoma[778] (17% of these patients develop bone mets, 5-year median survival is 16%).

Table 21-85 Sources of spinal epidural metastases causing cord compression

Site of primary	Series A	Series B*	Series C†
lung	17%	14%	31%
breast	16%	21%	24%
prostate	11%	19%	8%
kidney (renal-cell)	9%		1%
unknown site	9%	5%	2%
sarcoma	8%		2%
lymphoma	6%	12%	6%
GI tract	6%		9%
thyroid	6%		
melanoma	2%		4%
others (including multiple myeloma)	13%	29%‡	13%

* series B: retrospective study of 58 patients undergoing MRI evaluation for SEM[774]

† series C: 75 patients with SEM out of 140 patients evaluated prospectively for back pain[777]

‡ in series B, "other" includes GI, GU, skin, ENT, CNS

Presentation

Pain: the most common initial symptom. Occurs in up to 95% of patients with SEM[779, 780]. Types of pain:

- local pain: typically aching, experienced at the level of involvement. Increased pain with recumbency (especially at night) is characteristic
- radicular: tends to be sharp or shooting, referred into dermatome of the involved nerve root. Commonly bilateral in thoracic region
- mechanical: usually exacerbated by movement

Neck-flexion, straight-leg-raising, coughing, sneezing, or straining may also aggravate the pain.

Motor or autonomic dysfunction: the second most common presentation. Up to 85% of patients have weakness at the time of diagnosis. Leg stiffness may be an early symptom. Bladder dysfunction (urinary urgency, hesitancy or retention) is the most common autonomic manifestation; others include constipation or impotence.

Sensory dysfunction: anesthesia, hypesthesia, or paresthesias usually occur with motor dysfunction. Cervical or thoracic cord involvement may produce a sensory level.

Other presentations: pathologic fracture. Bone metastases can sometimes produce hypercalcemia (a medical emergency).

The greater the neurologic deficit when treatment is initiated, the worse the chances for recovery of lost function. 76% of patients have weakness by the time of diagnosis[774]. 15% are paraplegic on initial presentation, and < 5% of these can ambulate after treatment. Median time from onset of symptoms to diagnosis is 2 months[781].

Metastases to the upper cervical spine

For differential diagnosis, see *Foramen magnum lesions*, page 1212 and *Axis (C2) vertebra lesions* on page 1231.

Metastases to the C1-2 region comprise only ≈ 0.5% of spinal mets[782]. They typically present initially with suboccipital and posterior cervical pain, and as the lesion progresses patients develop a characteristic pain that makes it difficult to sit up (some will hold their heads in their hands to stabilize it). Possibly as a result of the capacious spinal canal at this level, only ≈11-15% of patients present with neurologic symptoms. 15% develop spinal cord compression[783], and quadriplegia from atlantoaxial subluxation occurred in ≈ 6%[783].

Anterior approaches for stabilization at this location are difficult. Pathologic fractures due to osteoblastic types of tumors (e.g. prostate, some breast) may heal with radiation treatment and immobilization. For others, good pain relief and stabilization may be achieved with radiation followed by posterior fusion[783].

EVALUATION AND MANAGEMENT OF EPIDURAL SPINAL METASTASES

There is no difference in outcome between lesions above or below the conus; thus spinal cord, conus medullaris, or cauda equina mets are considered together here as epidural spinal cord compression **(ESCC)**. Features that help distinguish conus lesions from cauda equina are shown in *Table 21-86*.

Table 21-86 Features distinguishing conus lesions from cauda equina lesions[784]

	Conus medullaris lesions	Cauda equina lesions
spontaneous pain	rare; when present, is usually bilateral & symmetric in perineum or thighs	may be most prominent symptom; severe; radicular type; in perineum, thighs & legs, back or bladder
sensory deficit	saddle; bilateral; usually symmetric; sensory dissociation	saddle; no sensory dissociation; may be unilateral & asymmetric

motor loss	symmetric; not marked; fasciculations may be present	asymmetric; more marked; atrophy may occur; fasciculations rare
autonomic symptoms (including bladder dysfunction, impotency…)	prominent early	late
reflexes	only ankle jerk absent (preserved knee jerk)	ankle jerk & knee jerk may be absent
onset	sudden and bilateral	gradual and unilateral

GRADING FUNCTION

There is prognostic significance in the presenting neurologic condition. Grading scales such as that of Brice and McKissock (*see Table 21-87*) have been proposed.

Table 21-87 Grading spinal cord function with spinal metastases (Brice & McKissock)[785]

Group	Grade	Description
1	mild	patient able to walk
2	moderate	able to move legs, but not antigravity
3	severe	slight residual motor and sensory function
4	complete	no motor, sensory, or sphincter function below level of lesion

DIAGNOSTIC TESTS

PLAIN X-RAYS

Most spinal mets are osteolytic, but at least 50% of the bone must be eroded before plain x-rays will be abnormal[786]. Not very specific. Possible findings: pedicle erosion (defect in "owl's eyes" AKA "winking owl sign" on LS or thoracic spine AP view) or widening, pathological compression fracture, vertebral body **(VB)** scalloping, VB sclerosis, osteoblastic changes (may occur with prostate Ca, Hodgkin's disease, occasionally with breast Ca, and rarely with multiple myeloma)

MRI IN EVALUATING SEM

The test of choice in most situations. Advantages of MRI over myelography[774]:

1. non-invasive. Doesn't require second procedure (C1-2 puncture) if

complete block
2. no risk of neurologic deterioration from LP in patient with complete block
3. detects lesions that do not cause bony destruction or distortion of the spinal subarachnoid space
4. up to 20% of patients with SEM have at least two sites of cord compression, MRI can evaluate region between two complete blocks, myelography cannot
5. demonstrates paraspinal lesions

Disadvantages of MRI versus myelography:
1. does not obtain CSF for cytological study
2. contraindicated with cardiac pacemaker or internal defibrillator

MRI findings in spinal epidural metastases:
1. vertebral mets are slightly hypointense compared to normal bone marrow on T1WI, and are slightly hyperintense on T2WI
2. axial cuts typically show lesion involving the posterior vertebral body with invasion into one or both pedicles
3. when myelopathy or radiculopathy are present, there is usually tumor extension into the spinal canal (may not occur in lesions presenting only with local pain)
4. DWI images may help differentiate osteoporotic compression fracture from pathologic fracture[787]

CT in evaluating SEM

Very good for bone detail. Often helpful for planning fusions. By itself, has low sensitivity for spinal cord compression by tumor. Sensitivity is increased with intrathecal contrast.

Positron emission tomography ***(PET)*** *scan*

PET scan using [18F]-fluorodeoxyglucose may be used for whole-body work-up for bone mets in patients with known cancer[788]. Sensitivity is high, but spatial resolution and specificity are low, so often must be used with CT and/or MRI.

Management

Patients are categorized into one of the three following groups below based on the rapidity and seriousness of the neurologic findings[784].

A metastatic work-up is undertaken as time permits (see *Metastatic work-up*, page 747) (a preliminary work-up, e.g. CXR and physical exam, may be all that can be initially obtained for patients in Group I, whereas more complete work-up can be done in others).

Group I

Signs/symptoms of new or progressive (hours to days) cord compression (e.g. urinary urgency, ascending numbness). These patients have a high risk of rapid deterioration and require immediate evaluation.

Management

1. dexamethasone **(DMZ)** (Decadron®): reduces pain in 85%, may produce transient neurologic improvement. Optimal dose is not known. No difference was found comparing 100 mg IV bolus to 10 mg[789]. Suggestion: 10 mg IV or PO q 6 hrs **x** 72 hrs, followed by lower dose of 4-6 mg q 6 hrs
2. radiographic evaluation
    A. plain x-rays of entire spine: 67-85% will be abnormal (*see above*)
    B. emergency MRI (see *MRI in evaluating SEM* above)
    C. **emergency myelogram**: if MRI cannot be done (include possible C1-2 puncture on the consent). Start with a so-called "**blockogram**" to R/O complete block: instill small volume of contrast (e.g. iohexol, *see page 122*) via LP and run the contrast all the way up the spinal column (CSF is usually xanthochromic with complete block, see *Froin's syndrome*, page 733)
        1. if there is not a complete block: with-draw 10 cc of CSF and send for cytology, protein & glucose. One may then inject more contrast to complete the study
        2. if complete block: do not remove CSF (pressure shifts via LP caused neurologic deterioration in ≈ 14% of patients with complete block[790], whereas there was no deterioration after C1-2 puncture)
            a. in some cases, contrast can be "squeezed" past a "complete" block by injecting 5-10 ml of room air through a millipore filter[791]

            OR

            b. perform a lateral C1-2 puncture (*see page 205*) and instill water soluble contrast to delineate the superior extent of the lesion

3. with myelography, epidural lesions classically produce **hourglass deformity** with smooth edges if block is incomplete, or **paintbrush effect** (feathered edges) if block is complete, unlike the sharp margins (**capping** or **meniscus sign**) of intradural extramedullary lesion, or fusiform cord widening of intramedullary tumors

D. bone scan if time permits. Abnormal in ≈ 66% of patients with spine mets

3. treatment based on results of radiographic evaluation
   A. if no epidural mass: treat primary tumor (e.g. systemic chemotherapy). Local radiation therapy **(XRT)** to bony lesion if present. Analgesics for pain
   B. if epidural lesion, either surgery or start XRT (usually 30-40 Gy in 10 treatments over 7-10 d with ports extending 2 levels above and below lesion). XRT is usually as effective as laminectomy with fewer complications (for further discussion see *Treatment for SEM*, page 747). Thus, surgery instead of XRT is considered only for the indications shown in *Table 21-88*
   C. urgency of treatment (surgery or XRT) is based on degree of block and rapidity of deterioration:
      1. if > 80% block or rapid progression of deficit: emergency treatment ASAP (if treating with XRT instead of surgery, continue DMZ next day at 24 mg IV q 6 hrs x 2 days, then taper during XRT over 2 wks)
      2. if < 80% block: treatment on "routine" basis (for XRT, continue DMZ 4 mg IV q 6 hrs, taper during treatment as tolerated)

Table 21-88 Indications for surgery for spinal metastases

Indications
1. unknown primary and no tissue diagnosis (CT guided needle biopsy is an option for accessible lesions). NB: lesions such as spinal epidural abscess can be mistaken for metastases[792]
2. spinal instability
3. deficit due to spinal deformity or compression by bone rather than by tumor (e.g. due to compression fracture with collapse and retropulsed bone)
4. radio-resistant tumors (e.g. renal-cell carcinoma, melanoma…) or progression during XRT (usual trial: at least 48 hrs, unless significant or rapid deterioration)
5. recurrence after maximal XRT
6. rapid neurologic deterioration
Relative contraindications
1. very radiosensitive tumors (multiple myeloma, lymphoma…) not previously radiated
2. total paralysis (Brice and McKissock group 4) > 8 hours duration, or inability to walk (B&M group > 1) for > 24 hrs duration (after this, there is essentially no chance of recovery and surgery is not indicated)

3. expected survival: ≤ 3-4 months
4. multiple lesions at multiple levels
5. patient unable to tolerate surgery: for patients with lung lesions, check PFTs

Group II

Mild and stable signs/symptoms of cord compression (e.g. isolated Babinski), or either plexopathy or radiculopathy without evidence of cord compression. Admit and evaluate within 24 hrs.

Management

1. for suspected ESCC, manage as in Group I except on less emergent basis. Use low dose dexamethasone **(DMZ)** unless radiographic evaluation shows > 80% block
2. for radiculopathy alone (radicular pain, weakness or reflex changes in one myotome or sensory changes in one dermatome): if plain x-rays show bony lesion then 70-88% will have ESCC on myelography. If the plain film is normal, only 9-25% will have ESCC. Obtain MRI or myelogram and manage as for suspected ESCC
3. for plexopathy (brachial or lumbosacral): pain is the most common early symptom, distribution not limited to single dermatome, commonly referred to elbow or ankle. May mask coexistent radiculopathy, distinguish by EMG (denervation of paraspinal muscles occurs in radiculopathy) or presence of proximal signs and symptoms (Horner's syndrome in cervical region, ureteral obstruction in lumbar region). Management:
   A. MRI is initial diagnostic procedure (CT if MRI unavailable): C4 through T4 for brachial plexopathy, L1 through pelvis for lumbosacral
   B. if CT shows bony lesion or paraspinal mass (with negative CT, plain films and bone scan are rarely helpful; however, if done, and plain x-ray shows malignant appearing bony lesion, or if bone scan shows vertebral abnormality, perform MRI or myelogram within 24 hrs) (give dexamethasone if ESCC suspected or MRI/myelogram delayed). Management as in Group I based on degree of block, XRT ports extended laterally to include any mass shown on CT
   C. if no bony nor paraspinal lesion on MRI/CT, primary treatment of plexus tumor; analgesics for pain

Group III

Back pain without neuro signs/symptoms. Can be evaluated as outpatient over several days (modify based on ability of patient to travel, reliability, etc.).

Management

1. plain spine x-ray (AP, lat, oblique)
   A. if focal bony pathology demonstrated: obtain MRI or myelogram (66% of patients with isolated LBP and X-ray abnormalities had SEM; in 81% with vertebral collapse > 50%, in 31% with pedicle erosion only, and in 7% with vertebral body lesion without collapse). Proceed as in Group I based on results of MRI/myelogram
   B. if plain films normal: bone scan (bone scan positive in up to 20% of patients with normal plain films with ESCC). Consider MRI or myelogram if bone scan abnormal in absence of benign x-ray lesion
2. CT: if bony lesion or paraspinal mass, proceed to MRI or myelogram, otherwise primary tumor treatment and analgesics

METASTATIC WORK-UP

The appropriateness of the following tests depends on the amount of time available as well as clinical information that may rule some primaries in or out.

1. CXR: to rule out lung primary or other mets to lung
2. CT of chest, abdomen and pelvis
3. serum prostate specific antigen **(PSA)** in males
4. mammogram in females
5. for multiple myeloma: *see page 741*
6. careful physical exam of lymph nodes

TREATMENT FOR SEM

TREATMENT GOALS AND OUTCOME

No treatment for SEM significantly prolongs life. Treatment goals are palliative: pain control, preservation of spinal stability, and maintenance of sphincter control and ability to ambulate.

The most important factor affecting prognosis, regardless of treatment modality, is ability to walk at the time of initiation of therapy. Loss of sphincter control is a poor prognosticator and is usually irreversible.

The main decision is between surgery + post-op XRT, or XRT alone. As yet,

no chemotherapy found useful for SEM (may help with primary). Surgery alone appears least effective for pain control (36%, compared to 67% for surgery + XRT, and 76% for XRT alone)[793]. Surgery has the attendant complications of anesthetic risk, post-op pain, wound problems in 11% (further complicated by radiation)[793], and mortality in 5-6% after laminectomy and 10% after anterior approach with stabilization[794]. Therefore, surgery appears best reserved for situations described in *Table 21-88*, page 745.

Deterioration in one of the 3 major criteria (pain, continence, ambulation) occurred in 26% of patients treated with laminectomy alone, 20% of laminectomy + XRT, and 17% of XRT alone (roughly comparable). There is a 9% incidence of spinal instability[793] following laminectomy without stabilization.

MEDICAL THERAPY

Chemotherapy is ineffective for SEM.

Bisphosphonates reduce the risk of vertebral compression fractures (VCF) by ≈ 50%, but the effect seems to abate after ≈ 2-3 years.

Promising agents undergoing trials include: denosumab, a RANK ligand (RANKL) inhibitor (*see page 994*) that may counteract RANKL which is overexpressed in response to lytic bony metastases[795]. The efficacy seems better than the bisphosphonate.

VERTEBROPLASTY/KYPHOPLASTY

Vertebroplasty/kyphoplasty (*see page 994*) reduces pain associated with pathologic fractures in up to 84%[796] with an associated increase in functional outcome[816]. Kyphoplasty appears to offer comparable pain relief to vertebroplasty with lower rates of cement leakage[816].

Relative contraindication: spinal cord compression. Unless the diagnosis has already been verified, a biopsy should be taken through one of the pedicles prior to injecting PMMA.

RADIATION THERAPY

Radiosensitive tumors: *Table 21-70*, page 708 lists radiosensitivity of metastatic tumors (to *brain* or spine). Other radiosensitive tumors that metastasize to the spine include: myxoid liposarcoma[797].

Treatment[798]: Dose: range = 25-40 Gy. Typical plan: 30 Gy delivered in 3 Gy fractions over 10 days (2 working weeks) to ports extending at least 1 vertebral

level above and below the extent o f the lesion. Timing: for initial treatment, try to start XRT within 24 hours of diagnosis; for post-op XRT, within about 14 days following surgery.

There is a theoretical risk of radiation induced edema causing or accelerating neurologic deterioration. This has not been born out by experimental studies with the usual small daily fractions utilized. Deterioration is more likely to be due to tumor progression[799]. The spinal cord is usually the dose limiting structure in treating SEM.

Increased doses are being made possible with the application of the added precision of stereotactic radiosurgery techniques to spinal metastases[800].

SURGICAL TREATMENT

See *Table 21-88*, page 745 for indications for surgery.

Pre-op embolization by interventional radiologist may facilitate resection with less blood loss for highly vascular tumors such as: renal-cell, thyroid, and hepatocellular. Blood supply is through the intercostal arteries, and care must be taken to avoid embolizing vessels providing significant blood supply to the spinal cord (especially the artery of Adamkiewicz (*see page 96*)).

TECHNIQUE

Laminectomy alone is poor for spinal metastases when the pathology is anterior to the cord because of poor access to the tumor and the destabilizing effect of laminectomy when metastatic involvement of the vertebral body is significant[801, 802].

In a randomized controlled trial by Patchell et al.[803], approaches directed at the location of the tumor (e.g. costotransversectomy, transthoracic approach…) with stabilization where necessary, produced better results than simple laminectomy, and surgery + XRT was superior to XRT alone (*see Table 21-89*). This study found a modest increase in survival, but more significant maintenance or regaining of lost ambulation. However, operative mortality with anterior decompression and stabilization was ≈ double (10%) that of laminectomy with (5%) or without (6%) stabilization in a literature review[794].

Solitary spinal metastases with indolent tumors (e.g. renal cell Ca) may be candi-dates for attempted cure with en bloc resection (total spondylectomy)[804, 805].

Laminectomy is still appropriate with isolated involvement of the posterior elements. For anterior pathology, if the posterior elements are intact, a transthoracic approach with corpectomy and stabilization (e.g. with

methylmethacrylate and Steinmann pins[806], or with cage graft and lateral plate) followed by XRT improves neurologic function in ≈ 75% and pain in ≈ 85%. A posterolateral approach (e.g. costotransversectomy) may be used for anterolateral tumor[807]. Combining a corpectomy and removal of the pedicle and posterior elements destabilizes the spine, therefore posterior instrumentation prior to performing the corpectomy is required, followed by cage graft[808-814]. To access a VB via a costotransversectomy, the rib of the like numbered VB and the one below need to be removed.

Table 21-89 Comparing surgery + XRT to XRT alone[803]

	XRT	Surgery + XRT
Ambulatory after treatment	57%	84%
Days ambulatory after treatment	13	122
Ambulatory after treatment when nonambulatory before treatment	19%	62%
Mean survival (days)	100	126

21.13. Neuroblastomas

Tumors arising from sympathetic ganglion[815]. May occur anywhere in the sympathetic nervous system, most commonly from adrenal gland (40%), followed by sympathetic ganglia of thoracic (15%), cervical (5%) and pelvic regions (5%). Neoplasms under this rubric include:

1. neuroblastomas: the most undifferentiated and aggressive in this group. Olfactory neuroblastomas are called esthesioneuroblastomas (discussed on *page 1230*)
2. ganglioneuroblastomas
3. ganglioneuromas

Presentation

May present with abdominal mass, local or radicular pain, or (with high thoracic or cervical tumors) Horner’s syndrome. Spinal cord compression may occur from invasion through the neural foramen, and scoliosis may occur. Catecholamine precursors (homo-vanillic acid (HVA), vanillylmandelic acid (VMA) and dopamine) may be excreted and cause HTN (can be assayed in

urine). Periorbital tumor metastases may produce raccoon's eyes (usually unilateral ecchymosis and proptosis). Many of the low-grade tumors regress spontaneously and never present.

21.14. References

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NOTES

22. Radiation therapy (XRT)

Introduction

Ionizing radiation includes x-rays and gamma rays (both of which transmit their energy via photons) and particulate radiation. The goal of XRT in treating tumors is to cause cell death or to stop cell replication. Photons impart critical energy to achieve this result by the photoelectric effect (at lower energies, < 0.05 MeV), by Compton scattering (at higher energies of 0.1-10 MeV, e.g. in linear accelerators and Gamma knives), or by pair-production (at the highest energies)[1]. In the Compton effect, the initial collision of the photon with an atom creates a free electron which then ionizes other atoms and breaks chemical bonds. The absorption of radiation by indirect ionization in the presence of water produces free radicals (containing an unpaired electron) which causes cellular injury (usually by damaging DNA) within the tumor.

For a discussion of radiation dosage and units, *see page 126*.

22.1. Conventional external beam radiation

Fractionation

The practice in which the total radiation dose is delivered in a series of smaller brief applications. This is one means of increasing the therapeutic ratio (the ratio of the effectiveness of XRT on tumor cells to that of normal cells). Radiation injury is a function of the dose, the exposure time, and the area exposed. Radiation oncologists refer to the four "R's" of radiobiology[2]:

1. **R**epair of sublethal damage
2. **R**eoxygenation of tumor cells that were hypoxic before XRT: oxygenated cells are more sensitive than hypoxic cells because oxygen combines with unpaired electrons to form peroxides which are more stable and lethal than free radicals
3. **R**epopulation of tumor cells following treatment
4. **R**edistribution (or reassortment) of cells within the cell cycle: cells in the mitotic phase are the most sensitive

Dosing

The biologically effective dose of fractionated radiation is often modeled by the linear-quadratic equation (LQ-model) shown in *Eq 22-1*, where D = the total dose of radiation, d = dose per fraction, and the factors α & β are used to describe the cell response to radiation. A high α/β ratio ≥ 10 is designated as early-responding tissue such as tumor cells, and a ratio ≤ 3 is considered late-responding tissue (mitotically quiescent), such as normal brain and also AVMs.

Linear quadratic equation

$$\text{biologically effective dose (Gy)} = D \times \left[1 + \frac{d}{\alpha/\beta}\right] \qquad \textbf{Eq 22-1}$$

22.1.1. Cranial radiation

Following surgery for tumor (craniotomy or spinal surgery), most surgeons wait ≈ 7-10 days before instituting XRT to the surgical site (allows initiation of healing).

Two CNS tumors that "melt away" with XRT but tend to recur later:

1. lymphoma
2. germ cell tumors

RADIATION INJURY AND NECROSIS

Radiation necrosis **(RN)** may mimic recurrent (or de novo) tumor both clinically and radiographically. Differences in prognosis and treatment make it important to distinguish between tumor and RN.

PATHOPHYSIOLOGY

As radiation is selectively toxic to more rapidly dividing cells, the two normal cell types within the CNS most vulnerable to RN are vascular endothelium (which have a turnover time of ≈ 6-10 mos) and oligodendroglial cells. Vascular injury may be the primary limiting factor to the tolerance of cranial XRT[3]. Injury from XRT occurs at lower doses when given concurrently with chemotherapy (especially methotrexate).

Radiation effects are divided into 3 phases[4]:

1. acute: occur during treatment. Rare. Usually an exacerbation of symptoms already present. Probably secondary to edema. Treat with ↑ steroids

2. <u>early delayed</u>: few weeks to 2-3 mos following completion of XRT. In spinal cord → Lhermitte's sign. In brain → post-irradiation lethargy & memory difficulties
3. <u>late delayed</u>: 3 mos-12 yrs (most within 3 years). Due to small artery injury → thrombotic occlusion → white matter atrophy or frank coagulative necrosis

Manifestations of radiation effects:

1. decreased cognition
   A. dementia may develop following XRT[5] in as little as 1 year post-XRT. Incidence was higher when doses of 25-39 Gy were given in fractions > 300 cGy[6]
   B. children: may attain lower IQ by ≈ 25 points, especially with > 40 Gy whole brain XRT. Measurable IQ differences occur in children radiated before age 7, but more subtle deficits occur even in older children[7]
2. radiation necrosis
3. injury to anterior optic pathways
4. injury to hypothalamic-pituitary axis → hypopituitarism → growth retardation in children (*see page 655* for radiation injury to pituitary)
5. primary hypothyroidism (especially in children)
6. may induce formation of new tumor: tumors most commonly identified as having increased incidence following radiation treatment are gliomas (including glioblastoma[8]), meningiomas[9], and nerve sheath tumors[10]. Skull base tumors have been reported following EBRT[11]
7. malignant transformation: e.g. after SRS for vestibular schwannomas (*see page 633*)
8. leukoencephalopathy: profound demyelinating/necrotizing reaction 4-12 mos after combined RXT and methotrexate, especially in children with acute lymphoblastic leukemia **(ALL)** and adults with primary CNS tumors

EVALUATION (DIFFERENTIATING RN FROM RECURRENT TUMOR)

IMHO Over the years many methods have been championed to differentiate radiation necrosis from recurrent high-grade glioma. Some are listed below. None have proven adequately reliable, and this may not even be a useful exercise. Tumor cells are frequently found on biopsy. The decision whether to reoperate is usually based on whether there is progressive mass effect (regardless of whether it is necrosis or tumor) taking into consideration the patient's neurologic condition, projected longevity, patient desires…

CT & MRI

Cannot reliably differentiate some cases of RN from tumor (especially astrocytoma; RN occasionally resembles glioblastoma).

MR spectroscopy (*see page 133*) was reliable in distinguishing pure tumor (elevated choline) from pure RN (low choline), but was less definitive with mixed tumor/necrosis[12].

DWI: mean ADCs were lower with recurrence (1.18 ± 0.13 X 10-3 mm/s) vs. necrosis (1.4 ± 0.17 X 10-3 mm/s)[13] (not all cases biopsy proven).

Nuclear brain scan

Some reports of success with thallium-201 and technetium-99m brain scans.

Computerized radionuclide studies

PET (positron emission tomography) scan: because positron emitting isotopes have short half lives, PET scanning requires a nearby cyclotron to generate the radiopharmaceuticals at great expense. Utilizing [18F]-fluorodeoxyglucose **(FDG)**, regional glucose metabolism is imaged and is generally increased with recurrent tumor, and is decreased with RN. Specificity for distinguishing RN from tumor recurrence is > 90%, but sensitivity may be too low to make it reliable[14]. Amino acid tracers such as [11C]methionine and [18F]tyrosine are taken up by most brain tumors[15], especially gliomas, and may also be used to help differentiate tumor from necrosis. Accuracy may be increased by fusing PET scan with MRI[16].

SPECT (single positron emission computed tomography): "poor man's PET scan". Uses radiolabeled amphetamine. Uptake depends on presence of intact neurons and the condition of cerebral blood vessels (including blood brain barrier). Decreased radionuclide uptake indicates necrosis, whereas tumor recurrence has no decreased uptake.

Treatment

Symptoms from any form of radiation toxicity often respond initially to steroids.

Reoperation and excision is appropriate if there is deterioration from mass effect, regardless of whether the mass effect is from recurrent tumor or RN (the decision to reoperate should be based on the patient's Karnofsky rating, *see page 1182*). Although some benefit has been shown, most reoperation studies are

biased because they often select the patients who are doing better.

Other forms of therapy include: hyperbaric oxygen and anticoagulation.

Patients with documented tumor recurrence (as opposed to RN) may also be considered for additional radiation (external beam, interstitial brachytherapy, or stereotactic radiosurgery **(SRS)**) or chemotherapy.

PREVENTION

Injury is dependent on total radiation dose, number of treatments or fractions (less damage occurs with more frequent small treatments), and volume treated.

Various studies to determine the tolerance of normal brain to XRT have estimated that 65-75 Gy given over 6.5-8 wks in 5 fractions/week is usually tolerated (radiation necrosis will occur in ≈ 5% after 60 Gy fractionated in 30 treatments over 6 weeks). Other studies have shown tolerance to 45 Gy for 10 fractions, 60 Gy for 35 fractions, and 70 Gy for 60 fractions[4].

22.1.2. Spinal radiation

SIDE EFFECTS

1. radiation myelopathy: *see below*
2. those due to overlap with GI tract: N/V, diarrhea
3. bone marrow suppression
4. growth retardation in children[17]
5. risk of developing cavernous malformations of the spinal cord (*see page 1106*)

RADIATION MYELOPATHY

Radiation myelopathy **(RM)** typically occurs in patients with spinal cord included in radiation therapy **(XRT)** ports used to treat cancer outside the spinal cord, includes breast, lung, thyroid, and epidural mets. Radiation neuropathy may occur with irradiation in the region of the axilla for carcinoma of the breast (*see page 795*). In the lower extremities, XRT for pelvic or bone tumors (e.g. of the femur) may produce lumbar plexopathy. In addition to permanent changes, radiation therapy may also produce spinal cord edema which may resolve after completion of radiation therapy.

EPIDEMIOLOGY

Incidence difficult to estimate due to the fact that the onset is typically delayed together with the poor survival of patients with malignant disease requiring XRT.

Most cases reported involve the cervical cord in spite of the higher frequency with which the thoracic cord is exposed to XRT (perhaps due to higher XRT doses to the head and neck and longer survival than with lung Ca)[18]. Delay between completion of XRT and onset of symptoms is usually ≈ 1 yr (reported range: 1 mos-5 yrs).

Important factors relating to the occurrence of RM include[18]:

1. rate of application (probably the most important factor)
2. total radiation dose
3. extent of cord shielding
4. individual susceptibility and variability
5. amount of tissue radiated
6. vascular supply to the region radiated
7. source of radiation

PATHOPHYSIOLOGY

Effects of XRT on the spinal cord that lead to RM are:

1. direct injury to cells (including neurons)
2. vascular changes, including endothelial cell proliferation → thrombosis
3. hyalinization of collagen fibers

CLINICAL

Clinical types of radiation myelopathy

Four clinical types have been described and are shown in *Table 22-1*.

Onset is usually insidious, but abruptness has also been described; the presentation often mimics epidural mets. First symptoms: usually paresthesias and hypesthesia of LEs, and Lhermitte’s sign. Then spastic weakness of LEs with hyperreflexia develops. A Brown-Séquard syndrome is not uncommon.

Approximately 50% of patients developing RM also have dysphagia from esophageal strictures requiring dilatations (the dysphagia often predates the myelopathy).

Table 22-1 Types of radiation myelopathy

Type	Description
1	benign form; commonly several mos following XRT (reported as late as 1 yr). Usually resolves completely within several mos. Mild sensory symptoms (frequently limited to a Lhermitte's sign) without objective neurological findings
2	injury to anterior horn cells → lower motor neuron signs in arms or legs
3	described only in experimental animals after doses larger than normal XRT. Complete cord lesion within hours due to injury to blood vessels
4	the type commonly reported. Chronic, progressive myelopathy (*see text*)

Evaluation

Essentially a diagnosis of exclusion. Radiographic imaging (CT, myelography) will be normal. MRI may show spinal cord infarction. The history of previous radiation is key. The differential diagnosis is included in *Acute paraplegia or quadriplegia* on page 1190.

Prognosis

Prognosis for Type 4 RM is poor. Usually progresses to complete (or near complete) cord lesion. Paraplegia and/or sphincter involvement are poor signs.

Prevention

Maximum recommended cord radiation dose depends on size of port, and varies with investigator. With large field techniques (> 10 cm of cord), the risk of RM is negligible with ≤ 3.3 Gy in 42 days (0.55 Gy/wk), and with small field techniques ≤ 4.3 Gy in 42 days (0.717 Gy/wk). Larger doses may possibly be given safely if fractionated over longer periods. Recommended upper limit: 0.2 Gy/fraction.

22.2. Stereotactic radiosurgery & radiotherapy

Key concepts:

- uses stereotactic localization to precisely focus therapeutic radiation on a lesion, a large dose given in a single treatment is called stereotactic radio *surgery*
- best accepted indication: AVM ≤ 3 cm diameter with compact nidus for which surgical removal is not appropriate (deep location, proximity to

eloquent brain)
- advantage: low immediate procedural morbidity
- disadvantages: delayed complications of radiation. With AVM: long latency (1-3 years) to obliteration creates period with risk of hemorrhage

The term “stereotactic radiosurgery” **(SRS)** describes the use of stereotactic localization to administer large radiation doses via multiple noncoplanar ports or arcs (producing a very steep radiation gradient) to a precise locus while exposing normal structures to safely tolerated doses. Unlike conventional external beam radiation therapy **(EBRT)**, the dose is usually administered in a single treatment session.

Using stereotactic techniques to administer fractionated radiation has been called stereotactic radio *therapy* (*see page 775*). Fractionation capitalizes on the differential response of normal tissue from tumor cells to radiation (see *Fractionation*, page 770).

Stereotactic radiosurgery is also increasingly being used for spine lesions[19].

INDICATIONS

In general, SRS is useful for well circumscribed lesions less than approximately **2.5-3** cm diameter (the “classic” lesion for which SRS is used is for appropriate AVMs, *see below*). For larger lesions, the radiation dose must be reduced because of anatomic and radiobiological constraints, and the precision of the stereotactic technique is offset due to overlap.

Published uses of stereotactic radiosurgery include:

1. AVMs: *see below*
2. tumors: *see below*
   A. vestibular schwannomas: *see below*
   B. pituitary adenomas: conventional EBRT (fractionated over ≈ 5 wks) is generally preferred to SRS as the initial form of XRT
   C. craniopharyngiomas
   D. pineal tumors
   E. metastases
   F. high grade gliomas: *see below*
   G. meningiomas of the cavernous sinus[20]
3. functional neurosurgery
   A. for control of chronic pain[21] including trigeminal neuralgia[22, 23] (*see page 555*)

B. pallidotomies for Parkinson's disease (*see page 535*): usually not a technique of choice because of inability to perform physiologic stimulation prior to lesioning to verify target location which may vary by several millimeters. May be a consideration for the rare patient who cannot undergo placement of a stimulating/lesioning needle (e.g. refractory coagulopathy)

4. for treating patients refusing open surgery for various conditions

AVMs

SRS is best accepted for the treatment of small (< 3 cm) AVMs that are deep or border on eloquent brain and have a "compact" (i.e. sharply demarcated) nidus[24-26]. This includes those incompletely excised with previous surgery. The radiation induces endothelial cell proliferation which produces thickening of the vascular wall and ultimately obliteration of the lumen over a period of ≈ 1-2 years. SRS is of no benefit for venous angiomas (*see page 1104*). For a comparison of treatment options for AVMs *see page 1102*.

Larger AVMs (up to 5 cm) have also been treated with SRS with some success. Tentorial dural AVMs (*see page 1109*) have also shown promising response to SRS[28].

Tumors

The use of SRS for tumors is controversial. It is not advisable for use on benign tumors in young patients because of possible delayed side-effects following radiation (see *Delayed morbidity*, page 778) (possible exception: vestibular schwannomas, *see below*).

Infiltrating tumors

Generally not indicated for infiltrating tumors, e.g gliomas (poorly defined tumor margins defeats the advantage of precisely localized radiation) although it has been used for recurrent lesions following traditional treatment (surgical excision and fractionated external beam radiation). One of the arguments for SRS in these tumors is the fact that 90% of recurrences are within the original radiographic solid tumor volume[29]. RTOG trial 9305 showed no benefit with upfront use of SRS added to EBRT and BCNU chemotherapy in treating glioblastoma (http://www.rtog.org/closedsummaries/9305.html).

Vestibular schwannoma

Possible indications for SRS for VS: poor operative candidates (due to poor medical condition and/or advanced age, some use > 65 or 70 yrs as a cutoff), patient refusing surgery, bilateral VSs, post-operative treatment of incompletely removed VSs that continue to grow on serial imaging, or recurrences following surgical removal (also see *Vestibular schwannomas* under *Results* below).

CONTRAINDICATIONS

Compressive tumors of the spinal cord or medulla: even with the sharp isodose fall-off curves of SRS, there is still significant radiation delivered within a few millimeters of the margins of the lesion. This, together with the slight swelling of lesions that commonly follows SRS creates significant risk of neurologic injury, especially over the long term (and long survival is even more likely with benign lesions in young individuals).

COMPARISON OF SRS TECHNOLOGIES

Various methods are available, differing mostly on the source of the radiation and the technique for increasing the dose delivered to the lesion. A photon beam that is produced by electron acceleration is called an x-ray, whereas if it is produced by natural radioactive decay it is called a gamma ray. Although photons are identical regardless of how they are produced, gamma rays have a narrower distribution of energy than x-rays. The spatial accuracy of the gamma knife may be slightly better than linac systems, but the small difference does not seem critical because the error inherent in selecting the target margins exceeds the typical linac imprecision of ± 1 mm[30]. The linac has greater flexibility in dealing with non-spherical lesions and is much more economical than the gamma knife. For small lesions (< 3 cm diameter) both photon and charged particle beam sources have similar results.

Gamma knife

Different sized collimators and exposure times, using more than one isocenter, and plugging collimators that would pass radiation thorough sensitive structures are used to modify the treatment plan.

Linac

Standard linacs usually require modifications to provide the required precision (e.g. precision bearings, external collimators…).

Different sized collimators, different beam energies (arc weighting), and

alterations of the arc paths and the number of arcs are used to modify treatments.

Stereotactic radiotherapy ***(SRT)***

AKA fractionated SRS. NB: there may be some confusion due to the similar names, and both use stereotactic localization, but stereotactic radio *therapy* is fractionated c.f. stereotactic radio *surgery* which is usually given in a single treatment. AVMs share some characteristics of what radiation oncologists call "late responding" lesions based on the linear quadratic model **(LQ-model)** (*see page 770*), and there is little rationale for fractionated protocols (although the LQ-model may not apply to SRS). Some slow growing tumors may also be similar to late responding tissue, but there may regions of hypoxic cells where XRT will be less effective, and where the reoxygenation phenomenon would improve response (see the *Four "R's" of radiobiology, page 770*). Also, if there is some uncertainty regarding the tumor margins on CT or MRI and there is the possibility that some normal brain may be included in the treatment plan (or fear that constricting the treatment margins would exclude some tumor) this is again a situation where tissue repair may make fractionation more advantageous.

Accelerated fractionation (2-3 fractions/d **x** 1 week) are being investigated but are not appropriate in the vicinity of radiosensitive structures and may be inconvenient and expensive. **Hypofractionation** (1 fraction/d **x** 1 week) may be a better compromise.

For malignancies, fractionated schemes will almost always improve effectiveness of XRT. Research into SRT employs various methods to reposition the stereotactic frame, including masks, dental molds, etc. Displacement errors can be as high as 2-8 mm with mask systems, whereas recommended tolerances are 0.3 mm and 3°.

Although the optimal protocol has not yet been determined, SRT may have significant advantages for pituitary adenomas, peri-chiasmal lesions, in children (where it is even more desirable to minimize radiation of the normal brain), and in vestibular schw-annomas considered for XRT where there is useful hearing.

Vestibular schwannomas (VS)

Conventional EBRT is relatively effective in controlling residual or unresectable VSs (*see page 633*). SRT adds precision, with reported local control rates **(LCR)** of 94-100%[31], comparable to that for SRS (with follow-up typically in 5-year range, which is short for these characteristically slow-growing tumors).

Rx: sample SRT protocol[31]: 6-MV Linac with a micromultileaf collimator

used to deliver 54 Gy in 30 fractions of 1.8 Gy prescribed to the 90% isodose line via 7-22 noncoplanar static fields or 4-6 noncoplanar dynamic arcs to a target defined as the tumor volume plus a margin of 1-3 mm.

Cranial nerve dysfunction: SRT has not been compared head-to-head with SRS, but preliminary results suggest it may be superior to SRT (*see page 632*).

TREATMENT PLANNING

For a selected isocentric radiation dose to be delivered to a given volume, computer simulation programs help radiosurgeons select the number of arcs or beams, collimator width, etc., to keep exposure of nearby normal brain to acceptable limits, and limit radiation to particularly sensitive structures. *Table 22-2* shows maximum recommended doses of various organs for a single fraction. In the brain, critical radiation sensitive structures include: optic vitreous, nerve, and chiasm, brain stem, and pituitary gland.

Cranial nerves: special sensory nerves (optic, vestibulocochlear) are the most radiosensitive. Somatic afferents (trigeminal), visceral efferents (facial), and somatic efferents (oculomotor, hypoglossal) are the next most radiosensitive[33].

SRS treatment may also have a deleterious effect in structures sensitive to swelling, such as brain stem. Most radiosurgeons decline to use SRS for lesions in the region of the optic chiasm. However, in general it is not the radiosensitive structures located at a distance from the lesion that are at greatest risk. Rather, it is that tissue included in the higher dose isocenters immediately adjacent to the lesion.

For the linac, optimal dose drop-off usually occurs when **≥ 500° total degree-arc** is used (e.g. 5 arcs of 100° each). Using more than 5 arcs rarely produces a significant difference out to the 20% isodose curve.

Table 22-2 Maximum recommended radiation dose of critical organs (delivered in a single fraction)

Structure	Maximum dose (cGy)	% of maximum (at a prescribed dose of 50 Gy)
eye lens (cataract induction begins at 500 cGy)	100	2%
optic nerve[32]	100	2%
skin in beam	50	1%
thyroid	10	0.2%
gonads	1	0.02%
breast	3	0.06%

Doses

Doses specify the amount of radiation delivered to the isocenter (or to a specified isodose curve, e.g. 18 Gy to the 50% isodose curve) and relating the isodose curve to a specific region of the lesion (e.g. at the edge of the AVM nidus). **Dose-volume relation**: the dose of radiation that can be tolerated is highly dependent on the volume being treated (larger treatment volumes require lower doses to avoid complications).

Dose selection is made based on known information or is estimated from dose-volume-relationship. If uncertain, err on the side of a lower dose. Previous XRT must also be taken into account by the radiation physicist. Adjacent structures within ≈ 2.5 mm of the target will receive injurious radiation and the total dose should reduced.

Target localization

CT: accuracy is never better than ≈ 0.6 mm which is the pixel size.

MRI: has 1-2 mm shift due to spatial distortion artifact from the magnet. If MRI is required to visualize the lesion, it may be better to use image fusion techniques with CT.

Stereotactic angiography: rarely required, and may even introduce errors in treatment planning. Stereotactic angiography should not be used alone because of problems including: the true geometry of the lesion cannot be fully appreciated, vessels may be obscured by other vessels or bone, etc.[34-37]. *Digital* subtraction angiography is even more problematic because it warps the image and requires an "unwarping" algorithm to be used for SRS.

Conformational planning

The shape of the treatment volume can be influenced by covering some sources (with gamma-knife units) or by choosing arcs with certain orientations (with linac based systems). Also, static and dynamic collimators have been developed.

Lesions that are not round or ellipsoid in shape may also be accommodated by using multiple isocenters. Lower total doses for each isocenter must then be used.

AVMs

If embolization is used before SRS, wait ≈ 30 days between the two procedures. DO NOT use radioopaque material in embolization mixture (*see page 1103*). Some experts find that target selection after embolization is extraordinarily difficult because of multiple small residual “nidi”.

A bolus-enhanced stereotactic CT is usually employed (except for those AVMs that are difficult to see on CT or when metal clips from previous surgery or radioopaque substance from embolization creates too much artifact). Caution with stereotactic angiography (*see above*).

A general consensus is that **15 Gy to the periphery** of the AVM is optimal (range: 10-25). At McGill with linac SRS, they use 25-50 Gy delivered to 90% isodose curve at the edge of the nidus. With Bragg-peak, complications occurred less frequently with doses ≤ 19.2 Gy compared to doses above that (this may reduce the obliteration rate or increase the latency period)[38].

Due to the fact that AVMs are benign lesions that are often treated in young patients, conformal planning is critical to avoid injury to nearby normal brain.

Tumors

Vestibular schwannomas (and meningiomas): For 1 isocenter: 10-15 Gy with the tumor at the 80% isodose line (current recommended maximum dose[39, 40]: **14 Gy**) is associated with a lower incidence of cranial nerve palsies than higher doses[41]. For 2 isocenters: treat 10-15 Gy at the 70% isodose line.

Metastases: Median dose of 15 Gy (range: 9-25 Gy) at the center with the tumor contained in the 80% isodose curve has been recommended. One literature review found a reported range of 13-18 Gy at the center with good local control[42].

RESULTS

AVMs

At 1 year, 46-61% of AVMs were completely obliterated on angiography, and at 2 years 86% were obliterated. There was no reduction in size in < 2% of cases. Smaller lesions have higher obliteration rates (with Bragg-peak in AVMs < 2 cm diameter, 94% thrombosed at 2 yrs, and 100% at 3 yrs[38]). AVMs > 25 mm diameter have only ≈ 50% chance of obliteration with 1 SRS treatment.

Although the immediate “procedural” mortality is 0%, Bragg-peak proton beam treatment of AVMs affords no protection against hemorrhage in the first

12-14 months following treatment[26] (the so-called "**incubation period**"); this is similar to the 12-24 month latency for photon radiation[24]. Hemorrhages have occurred during the incubation period even in AVMs that had never bled before[38], and the question has been raised whether a partially thrombosed AVM is more likely to bleed because of increased outflow resistance.

Factors associated with treatment failures include[43]: incomplete angiographic definition of the nidus (the most frequent factor, responsible for 57% of cases), recanalization of the nidus (7%), masking of nidus by hematoma, and a theorized "radiobiological resistance". In some, no discernible reason for failure could be identified. In this series the complete obliteration rate was ≤ 64%, possibly because arteriography was heavily relied upon for treatment planning instead of emphasizing stereotactic CT.

If AVM persists 2-3 yrs after SRS, retreatment with SRS is an option[43] (usually the residual is smaller).

Vestibular schwannomas

In 111 tumors ≤ 3 cm in size[44], 44% decreased in size, 42% did not change, and 14% increased. Although retardation of growth is observed in the majority of cases, long-term results are not available to fully assess therapeutic efficacy and complication rate at this time[45]. Use in <u>recurrent</u> VSs following microsurgery is endorsed by some (*see page 633*). Also see *Outcome & follow-up*, page 631 for a comparison of outcomes (including cranial nerve dysfunction) with SRS versus microsurgery.

Gliomas

Median survival for large GBMs is so poor that SRS did not appear to have any benefit. Following SRS for gliomas, there is rarely reduction of enhancing volume (it is more common to have *enlargement*, sometimes with increased neurologic deficit).

Metastases

There has not been a randomized study to compare surgery to SRS. *See page 710* for comparison of outcomes with cerebral mets with various treatments including SRS. Radiographic local control rate of ≈ 88% (reported range: 82-100%) has been cited[42].

The advantage of SRS is that there is no risk from the treatment of

hemorrhage, infection, or mechanical spread of tumor cells. Disadvantages include not obtaining tissue for diagnosis (11% of the time the lesions may not be mets, *see page 707*).

No significant difference has been found with SRS between tumors considered "radiosensitive" and those that are "radioresistant" as defined by standards developed for EBRT (see *Table 21-70*, page 708) (however, histology may affect the *rate* of response). The lack of significance of "radioresistance" may be due in part to the fact that the sharp dose drop-off with SRS allows higher doses to be delivered to tumors than would be used with EBRT.

Supratentorial control is better than infratentorial. Also, there is no significant difference in local control between single and dual mets. The RTOG has identified 3 or fewer mets as a more favorable prognosticator.

TREATMENT MORBIDITY AND MORTALITY

Immediate morbidity

Immediate mortality from the actual treatments themselves is probably zero. Morbidity: all but ≈ 2.5% of patients were discharged home within 24 hrs. Many centers do not admit patients overnight. Some immediate adverse reactions include[46]:

1. 16% of patients require analgesics for post-procedural headaches and antiemetics for nausea/vomiting
2. at least 10% of patients with subcortical AVMs had focal or generalized seizures within 24 hrs of treatment (only one was on subtherapeutic AEDs. All were controllable with additional AEDs)

Premedication: The Pittsburgh Gamma Knife group gives methylprednisolone 40 mg IV and phenobarbital 90 mg IV immediately after the radiation dose to patients with tumors or AVMs to reduce these adverse effects[46].

Delayed morbidity

Long-term morbidity directly related to the radiation may occur, and just as with conventional XRT, is more frequent with larger doses and treatment volumes. Another risk particular to AVMs is that of hemorrhage during the latency period, which is 3-4% during the first year and is not higher following SRS. Radiation complications 47:

1. white matter changes: occurred 4-26 mos (mean 15.3) post-SRS. Seen on

imaging (high intensity on MRI T2WI, or low density on CT) in ≈ 50% of patients, symptomatic in only 20% of patients[38]. Associated with radiation necrosis in ≈ 3% of cases

2. vasculopathy: diagnosed by narrowing seen on angiography or by ischemic changes on imaging in ≈ 5% of cases
3. cranial nerve deficits: occur in ≈ 1% of all cases. Incidence is higher with tumors of CPA or skull base
4. induced tumors:
   A. malignant: only 6 reported malignant tumors in over 80,000 radiosurgical procedures for benign disease[48]. Estimated incidence: < 1 in 1000. Includes GBM, malignant degeneration of a schwannoma…
   B. meningiomas: 0.7% chance of developing this within 10 years of XRT in a series with 2 cases identified[A] in 1333 patients contacted (out of 2500 treated)[50] (risk was 1.9% in another series[51])

A. meeting the criteria of Cahan et al.[49] for XRT induced tumors

5. normal perfusion pressure breakthrough[52]: classically occurs following conventional microsurgery for AVMs (*see page 1104*), it has also been described following SRS[53]

22.3. Interstitial brachytherapy

Technique whereby radioactive implants are used to deliver locally high doses of radiation directly to tumors while exposing nearby normal brain to less toxic doses. At present, the numbers are too small and the follow-up too short to determine the efficacy of interstitial brachytherapy[54]. Controlled prospective studies have not yet been completed.

Interstitial brachytherapy **(IB)** may reduce the rate of tumor growth, but it rarely produces clinical improvement. Patients are generally not considered for IB unless their Karnofsky score is ≥ 70.

Techniques include:

1. insertion of high activity iodine-125 pellets which remain in place (either

by conventional open surgery or by stereotactic technique)

2. insertion of catheters (so-called afterloading catheters) containing radioactive source (such as gold or I^{125}) by stereotactic technique, which are then removed at a predetermined time (usually 1-7 days)
3. instillation of radioactive liquids (e.g. phosphorous isotope) into a cyst cavity

I^{125} has several characteristics that favor its use: it emits low-energy gamma rays which are absorbed by surrounding tissues minimizing radiation exposure of the normal brain, medical personnel and visitors. It is available as low-activity (< 5 mCi) or high-activity (5-40 mCi) seeds.

Treatment planning is devised to deliver 60 Gy to the edge of a volume that extends 1 cm beyond the contrast-enhancing tumor, with variations included to spare radiosensitive structures (e.g. optic chiasm). Usual delivery rates are 40-50 cGy/hr to the tumor margin (30 cGy/hr is the critical dose for cessation of human tumor growth) requiring that the seeds stay in the afterloading catheter ≈ 6 days.

Radiation necrosis

Symptomatic radiation necrosis **(RN)** occurs in ≈ 40% of cases, and may occur as early as several months after IB. It may be impossible to differentiate from recurrent tumor in many cases. Symptomatic treatment is often achieved with increased corticosteroid dosages. Continued neurologic deterioration may require craniotomy.

Outcome

IB is often used as a “last ditch” effort in a patient with a recurrent malignant tumor who has received maximal external beam irradiation and who is not a candidate for re-operation (as expected, the results in patients with such poor prognoses are not good). However, patients eligible for IB are usually better than those who are not candidates, and this may bias the results towards a better outcome[55]. Some studies with early (primary treatment) use have shown possible benefit[56].

22.4. References

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NOTES

23. Stereotactic surgery

Stereotactic (Greek: *stereo* = 3-dimensional, *tactic* = to touch) surgery was used for surgery performed in humans, usually for thalamic lesioning to treat Parkinsonism (see *Surgical treatment of Parkinson's disease*, page 532), where the target site to be lesioned was located relative to landmarks with intraoperative pneumoencephalography or contrast ventriculography. Use of this procedure fell off dramatically in the late 1960's with the introduction of L-dopa for Parkinsonism[1].

Current techniques would be more appropriately termed image-guided stereotactic surgery. Usually performed under local anesthesia (except in certain patients, e.g. some pediatrics). In the first part of the procedure, a CT scan or MRI (or occasionally, angiogram) is performed with a localizing device affixed to the patient's head, allowing the target to be precisely localized in space. Frameless systems used bony landmarks and sometimes fiducial markers to register the patient's skull relative to radiographic images (CT or MRI scans).

The second part of the procedure utilizes a set of guides oriented to the same coordinate system to direct biopsy needles, etc., to the target location. At this point, different stereotactic systems will require that the second part of the procedure be completed in the CT scan suite, or may permit it to be performed in the O.R.

Advantages of completing the procedure in the CT scan suite include:

1. verification of instrument placement at the desired target
2. immediate identification of problems such as hemorrhage
3. selection of entirely new coordinates if the first set yields undesirable results (some systems, such as the Leksell, permit coordinates to be read directly off the printed CT scan images)

Disadvantages of completing the procedure in the CT scan suite include:

1. longer time commitment of the CT scanner
2. possibly less sterile conditions
3. the need to get other equipment from the O.R. that is forgotten or needed for a unique reason (adds time to the procedure)
4. need to move the patient to the O.R. if a complication develops needing

emergent craniotomy

5. difficult to use for procedures much more extensive than twist drill or bull hole

INDICATIONS FOR STEREOTACTIC SURGERY

1. biopsy (also, *see below*)
   A. deeply located cerebral lesions: especially near eloquent brain
   B. brain stem lesions: may be approached through the cerebral hemisphere[2]
   C. multiple small lesions (e.g. in some AIDS patients, *see page 367*)
   D. patient medically unable to tolerate general anesthesia for open biopsy
2. catheter placement
   A. drainage of deep lesions: colloid cyst, abscess
   B. indwelling catheter placement for intratumoral chemotherapy
   C. radioactive implants for interstitial radiation brachytherapy[3]
   D. shunt placement: for hydrocephalus (rarely used) or to drain cyst
3. electrode placement
   A. depth electrodes for epilepsy
   B. "deep brain stimulation" for chronic pain (requires electrophysiologic stimulation)
4. lesion generation
   A. movement disorders: Parkinsonism (*see page 534*), dystonia, hemiballismus
   B. treatment of chronic pain
   C. treatment of epilepsy (rarely used)
5. evacuation of intracerebral hemorrhage
   A. using an Archimedes' screw device[4, 5]
   B. with adjunctive urokinase[6, 7] or recombinant tissue-plasminogen activator[8] (*see page 1130*)
6. stereotactic "radiosurgery" (see *Stereotactic radiosurgery & radiotherapy*, page 773)
7. to localize a lesion for open craniotomy (e.g. AVM[9], deep tumor)
   A. using a ventricular-type catheter
   B. using a blunt biopsy needle or introducer[10]
   C. systems using visible light laser beam for guidance

8. transoral biopsy of C2 (axis) vertebral body lesions[11]
9. “experimental” or unconventional applications
   A. stereotactic clipping of aneurysms[12]
   B. stereotactic laser surgery
   C. CNS transplantation[13]: e.g. for Parkinsonism (*see page 533*)
   D. foreign body removal[14]

STEREOTACTIC BIOPSY

This section presents information regarding stereotactic brain biopsy **(SBB)** in general. For SBB in specific conditions, see the index entry for that condition. May be performed under local or general anesthesia. For indications, *see above*.

Contraindications

1. coagulation disorders
   A. coagulopathies: bleeding diatheses, iatrogenic (heparin or coumadin)
   B. low platelet count **(PC)**: PC < 50,000/ml is an absolute contraindication, it is desirable to get the PC ≥ 100,000
2. inability to tolerate general anesthesia and to cooperate for local anesthesia

Yield

The yield rate (i.e. the ability to make a diagnosis from a SBB) reported in large series in the literature ranges from 82-99% in nonimmunocompromised **(NIC)** patients, and is slightly lower in AIDS patients at 56-96%. Higher yield rates in AIDS may result from improved surgical technique and histologic evaluation[15].

The yield rate is higher for lesions that enhance with contrast on CT or MRI (99% in NIC patients) than with lesions that do not enhance (74%)[16].

Complications

The most frequent complication is hemorrhage, although most are too small to have clinical impact. The risk of a *major* complication (mostly due to hemorrhage) in NIC patients ranges from 0-3% (with most < 1%), and 0-12% in AIDS[16]. Higher complication rates seen in AIDS patients in some series may be due to reduced platelet count or function, and to vessel fragility in primary CNS lymphoma. In NIC patients, multifocal high grade gliomas had the highest

complication rate.

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NOTES

24. Peripheral nerves

The peripheral nervous system **(PNS)** consists of those structures (including cranial nerves III-XII, spinal nerves, nerves of the extremities, and the cervical, brachial and lumbosacral plexi) containing nerve fibers or axons that connect the central nervous system **(CNS)** with motor and sensory, somatic and visceral, end organs[1].

Table 24-1 Muscle grading (modified Medical Research Council system)

Grade	Strength	
0	no contraction (total paralysis)	
1	flicker or trace contraction (palpable or visible)	
2	active movement with gravity eliminated	
3	active movement through full ROM against gravity	4- slight resistance
4	active movement against resistance; subdivisions →	4 moderate resistance
5	normal strength (against full resistance)	4+ strong resistance
NT	not testable	

Muscle strength grading usually employs the Royal Medical Research Council of Great Britain **(MRC)** scale[2], a common modification of which is shown in *Table 24-1*. Muscle stretch reflexes may be graded as shown in *Table 24-2*[2].

Upper motor neuron vs. lower motor neuron

Lower motor neurons **(LMN)** (first-order motor neuron): cell bodies (soma) reside in spinal cord (in anterior gray matter) or in brainstem (for cranial nerve motor nuclei). Axons connect directly to neuromuscular junction of muscles.

Upper motor neurons **(UMN)** (second-order motor neurons): some soma reside in the primary motor cortex (precentral gyrus) of the brain. Axons project to LMNs.

See *Table 24-3* for comparison of weakness due to UMN vs. LMN.

Table 24-2 Muscle stretch reflex (deep tendon reflex) grading scale

Grade	Definition
0	no contraction (total paralysis)

0.5+	elicitable only with reinforcement*
1+	low normal
2+	normal
3+	more brisk than normal (hyperreflexic)
4+	hyperreflexic with clonus
5+	sustained clonus

* In the LEs, reinforcement consists of having the patient hook the tips of the fingers of the left hand into the tips of the hooked fingers of the right hand and pulling **(Jendrassik maneuver)**. Reinforcement in the UEs consists of having the patient clench their teeth

Table 24-3 Upper vs. lower motor neuron paralysis

	Upper motor neuron paralysis	Lower motor neuron paralysis
possible etiologies	stroke (motor strip, internal capsule…), spinal cord injury, cervical spondylotic myelopathy	herniated intervertebral disk, nerve entrapment syndrome, polio, progressive muscular atrophy (PMA)
muscle tone	initially flaccid; later spastic with clasp-knife resistance	flaccid
tendon reflexes	hyperactive; clonus may be present	absent
pathologic reflexes (e.g. Babinski, Hoffman)	present (after days to weeks)	absent
muscle manifestations	spontaneous spasms may occur; some atrophy of disuse may occur	fibrillations*, fasciculations*. Atrophy after days to weeks due to trophic influence

*Fasciculations vs. fibrillations

Fasciculations are coarse muscle contractions that are visible to the naked eye, whereas fibrillations are not visible and require EMG to detect (AKA fibrillation *potentials* - *see page 270*).

Fasciculations represent discharge of a group of muscle fibers (all or part of an entire motor unit), and occur most often in diseases involving anterior horn cells, including:

1. amyotrophic lateral sclerosis (ALS): *see page 65*
2. spinal muscular atrophy: *see page 1191*
3. polio
4. syringomyelia

MUSCLE INNERVATION

Table 24-4 Muscle innervation - shoulder & upper extremity *

	Muscle	Action to test	Roots†	Trunk‡	Cord§	Nerve
	deep neck	flex, ext, rotation of neck	C1-4	–	–	cervical
	trapezius	elevates shoulder, adbucts arm > 90°	XI, C3, 4			(spinal acc + roots)
	diaphragm	inspiration	C3-5			phrenic
•	serratus anterior	forward shoulder thrust	C5-7	–	–	long thoracic
	levator scapulae	elevate scapula	C3, 4, **5**			dorsal scapular
	rhomboids	adduct & elevate scapula	C4, 5			" " "
	supraspinatus	abduct arm (15-30°)	C4, **5**, 6	S		suprascapular
•	infraspinatus	exorotation of humerus	**C5**, 6	S	–	" " "
	latissimus dorsi	adduct arm	C5, 6, **7**, 8			thoracodorsal
	teres major, subscapu-laris	" " "	C5-7			subscaspular
•	deltoid	abduct arm (30-90°)	**C5**, 6	S	P	axillary
	teres minor	exorotate & adduct humerus	C4,5			" "
•	biceps brachii	flex forearm (with hand supi-nated), & supinate forearm	**C5**, C6	S	L	musculocutaneous
	coracobrachialis	flex humerus at shoulder	C5-7			" " "
	brachialis	flex forearm	C5, 6			" " "
•	flexor carpi ulnaris	ulnar flexion of wrist	C7, **8**, T1	M, I	M	ulnar
•	flexor digitorum profun-dus III & IV (ulnar part)	flex distal phalanx of Dig 4-5	C7, **8**, T1	M, I	M	" "
	adductor pollicis	thumb adduction	C8, **T1**		M	" "
	abductor digiti minimi	abduction Dig 5	C8, T1		M	" "
	opponens digiti minimi	opposition Dig 5	C7, 8, T1			" "
	flexor digiti minimi brevis	flexion Dig 5	C7, **8**, **T1**		M	" "
•	interossei	flex proximal phalanx, extend 2 distal phalanges, abduct or adduct fingers	C8, **T1**	I	M	" "
	lumbricals 3 & 4	flex proximal phalanges & extend 2 distal phalanges of Dig 4-5	C7, **8**			" "
•	pronator teres	forearm pronation	C6,7	S,M	L	median
•	flexor carpi radialis	radial flexion of wrist	" "	S,M	L	" "
	palmaris longus	wrist flexion	C7, 8, T1			" "
•	flexor digitorum superfi-cialis	flexion middle phalanx Dig 2-5, flex wrist	C7, **8**, T1	M, I	M	" "
•	abductor pollicis brevis	abduct thumb metacarpal	C8, **T1**	I	M	" "
	flexor pollicis brevis	flex prox phalanx thumb	C8, **T1**			" "
•	opponens pollicis	opposes thumb metacarp	C8, **T1**	I	M	" "
	lumbricals 1 & 2	flex proximal phalanx & ex-tend 2 distal phalanges Dig 2-3	C8, **T1**			" "

•	flexor digitorum profundus I & II (radial part)	flex distal phalanx of Dig 2-3; flex wrist	C7, **8**, T1	M, I	M	anterior interosseous
•	flexor pollicis longus	flex distal phalanx thumb	C7, **8**, T1			" " "
•	triceps brachii	forearm extension	C6, **7**, 8	all	P	radial
•	brachioradialis	forearm flexion (with thumb pointed up)	C5, **6**	S	P	" "
•	extensor carpi radialis	radial wrist extension	C5, **6**	S,M	P	" "
•	supinator	forearm supination	C6, 7	S	P	" "
•	extensor digitorum	extension of wrist & phalanges of Dig 2-5	**C7**, C8	M, I	P	posterior interosseous **(PIN)**
	extensor carpi ulnaris	ulnar wrist extension	**C7**, C8			" " "
•	abductor pollicis longus	abduction thumb metacarpal & radial wrist extens.	**C7**, C8	M, I	P	" " "
	extensor pollicis brevis & longus	thumb extension & radial wrist extension	**C7**, C8			" " "
	extensor indicis proprius	extension Dig 2 & wrist extension	**C7**, C8			" " "
	pectoralis major: clavicular head	push arm forward against resistance	**C5**, 6			lateral pectoral
	pectoralis major: sternocostal head	adduct arm	C6, **7**, 8			lateral & medial pectoral

* NB: items marked with a bullet (•) are clinically important muscle/nerves.
NB: Dig → U.S. digit numbering convention: 1=thumb, 2=index finger, 3=middle, 4=ring, 5=little.

† Major innervation is indicated in **boldface**. Differing opinions exist, most shown are based on reference[3].

‡ **Trunk** (trunks of brachial plexus): S = superior, M = middle, I = inferior, all = all three.

§ **Cord** (cords of brachial plexus): P = posterior, L = lateral, M = medial.

Thumb

Flexion/extension: occurs in the plane of the palm.
Abduction/adduction: occur in a plane at right angles to palm.
Opposition: bringing the thumb across the hand.

Table 24-5 The 3 innervations of the thumb

Action	Nerve	Muscle(s)
abduction, flexion, opposition*	median	abductor pollicis brevis, flexor pollicis brevis, opponens pollicis
adduction	ulnar	adductor pollicis
extension	radial†	extensor pollicis brevis & longus

* occasional anomalous innervation by ulnar nerve

† via the posterior interosseous nerve

Table 24-6 Muscle innervation - hip & lower extremity *

	Muscle	Action	Roots†	Plexus‡	Nerves
•	iliopsoas§	hip flexion	**L1, 2**, 3	L	femoral & L1, 2, 3
	sartorius	hip flex & thigh evert	L2, 3		femoral
•	quadriceps femoris	leg (knee) extension	L2, **3, 4**	L	" "
	pectineus	thigh adduction	L2, 3		obturator
•	adductor longus	" " "	**L2, 3**, 4	L	" "
	adductor brevis	" " "	L2-4		" "
	adductor magnus	" " "	L3, 4		" "
	gracilis	" " "	L2-4		" "
	obturator externus	thigh adduction & lateral rotation	L3, 4		" "
•	gluteus medius/minimus	thigh abduction & medial rotation	**L4, 5**, S1	S	superior gluteal
	tensor fasciae lata	thigh flexion	L4, 5		" " "
	piriformis	lateral thigh rotation	L5, S1		" " "
•	gluteus maximus	thigh abduction (patient prone)	**L5, S1**, 2	S	inferior gluteal
	obturator internus	lateral thigh rotation	L5, S1	S	muscular branches
	gemelli	" " " "	L4, 5, S1	S	" " "
	quadratus femoris	" " " "	L4, 5, S1	S	" " "
•	biceps femorisΔ	leg flexion (& assist thigh extension)	L5, **S1**, 2		sciatic (trunk)
•	semitendinosusΔ	" " " "	L5, **S1**, 2		" " "
•	semimembranosusΔ	" " " "	L5, **S1**, 2		" " "
•	tibialis anterior	foot dorsiflexion & supination	L4, **5**¶	S	deep peroneal
•	extensor digitorum longus	extension toes 2-5 & foot dorsiflexion	**L5**, S1		" " "
•	extensor hallucis longus (EHL)**	great toe extension & foot dorsiflexion	**L5**¶, S1	S	" " "
•	extensor digitorum brevis	extension great toe & toes 2-5	**L5**, S1	S	" " "
•	peroneus longus & brevis	P-flex pronated foot & eversion	L5, S1	L/S	superficial peroneal
•	posterior tibialis	P-flex supinated foot & inversion	L4, 5	S	tibial
	flexor digitorum longus	P-flex sup foot, flex terminal phalanx toes 2-5	L5, **S1, 2**		" "
	flexor hallucis longus	P-flex sup foot, flex terminal phalanx great toe	L5, **S1, 2**		" "
	flexor digitorum brevis	flex mid phalanx toes 2-5	S2, 3		" "
	flexor hallucis brevis	flex proximal phalanx great toe	L5, S1, 2		" "
•	gastrocnemius	knee flexion, ankle P-flex	**S1**, 2	S	" "
	plantaris	" " " " "	**S1**, 2		" "
•	soleus	ankle P-flex	**S1**, 2	S	" "
•	abductor hallicus††	(cannot test††)	**S1**, 2	S	
	perineal & sphincters	voluntary contract pelvic floor	S2-4		pudendal

* Abbreviations: P-flex = plantarflexion, D-flex = dorsiflexion, phlnx = phalanx.

† Major innervation is indicated in **boldface** type. E.g. when roots are shown as L4, **5**, this indicates L5 is the main innervation, but both L4 & L5 contribute.

‡ **Plexus**: L = lumbar, S = sacral

§ iliopsoas is the term for the combined iliacus and psoas major muscles

Δ "**hamstrings**": familiar term for the grouped: semitendinosus and semimembranosus (together, the medial hamstrings) and the biceps femoris (lateral hamstrings)

¶ although many references, including some venerable ones, cite AT as being primarily L4, many clinicians agree that L5 innervation is probably more significant

** EHL is the best L5 muscle to test clinically (although S1 radiculopathy can also weaken this muscle)

†† abductor hallicus cannot be tested clinically, but is important for EMG

24.1. Some basic points about peripheral nerve injury/surgery

NERVE ACTION POTENTIALS

Stimulating a healthy nerve fiber with an electrical stimulus of an amplitude and duration that exceeds its threshold will produce a conducted impulse, or nerve action potential **(NAP)**[4 (p 103)]. Medium-sized axons (fibers) have a lower threshold than large ones which have lower threshold than small or fine axons[4 (p 103)].

Use of NAP with lesion in continuity

There is some degree of continuity in ≥ 60% of nerve injuries[4 (p 104)].

For a lesion in continuity **(LIC)**, if surgical repair is needed, it may be too late if one waits until there is failure of anticipated clinical improvement. Presence of a NAP (regardless of amplitude or latency) distal to an LIC in the first few months after an injury usually indicates that operative intervention will not be needed. For recommended timing to obtain NAP recording, *see Table 24-7*[4 (p 106)].

Table 24-7 Recommended timing to obtain NAP recording

Injury	Timing
relatively focal contusions	2-4 months
stretch injuries (esp. brachial plexus)	4-5 months
partial injuries & entrapments, compressive lesions and tumors	any time
to identify an area of conduction block (regardless if lesion is from neuropraxia, axonotmesis, or neurotmesis)	acutely

TIMING OF SURGICAL REPAIR

The longer the distance from the injury site to the functional unit to be reinnervated, the *earlier* surgical intervention should be considered[4 (p 74].

24 month rule[4 (p 74)]: after 24 months of denervation, most muscles cannot recover useful function even with reinnervation. Exceptions: facial muscles, large bulky muscles such as biceps, brachialis, gastrocs, and some lesions in

continuity with some preserved innervation.

24.2. Brachial plexus

Formed by ventral rami (the dorsal rami innervate the paraspinal muscles), most commonly of nerve roots C5-T1 (schematically depicted in *Figure 24-1*).

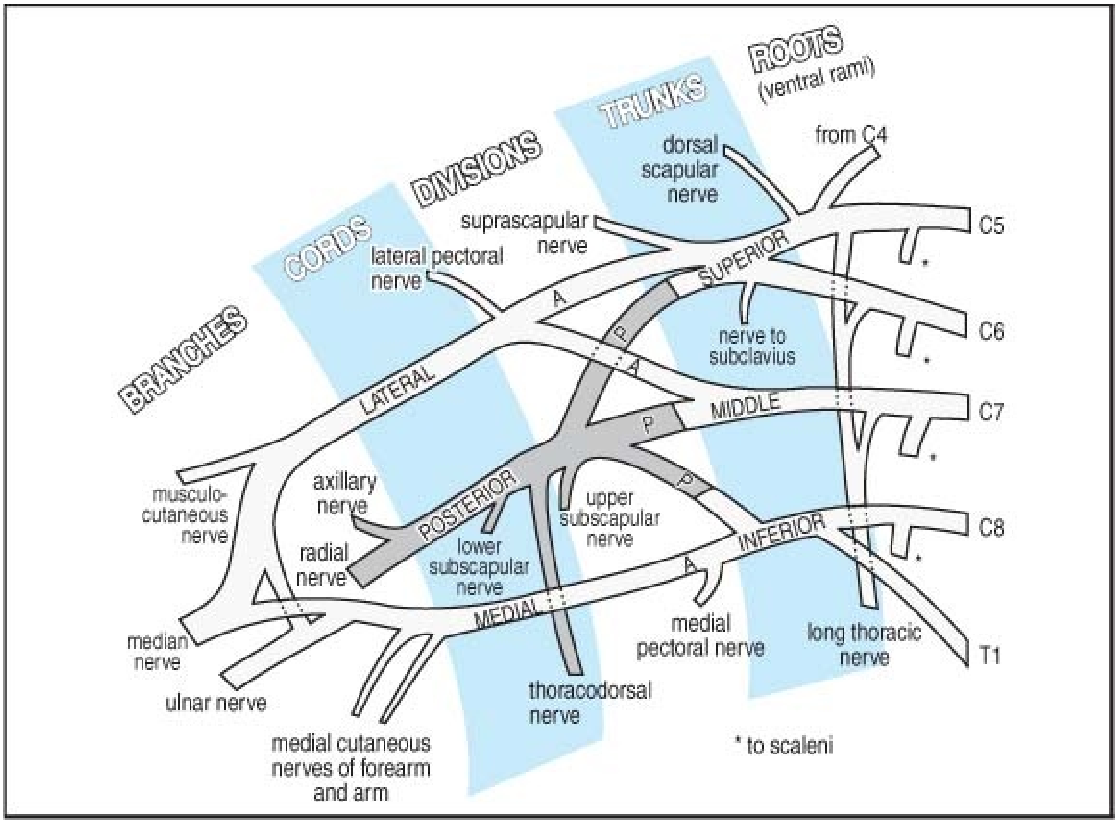

Figure 24-1 Schematic diagram of the brachial plexus
(By Permission: Churchill Livingstone, Edinburgh, 1973, R. Warwick & P. Williams: Gray's Anatomy 35th Edition © Longman Group UK Limited)

BRACHIAL PLEXUS BRANCHES

Table 24-4 shows action, etc. of specific muscles. Also see *Figure 24-1*. "↘" indicates that the nerve supplies the muscles listed; "↪" denotes a branch of the preceding nerve.

Radial nerve (C5-C8)

See *Figure 24-2*. Radial nerve (and its branches) innervate the extensors of arm and forearm:

- triceps (all 3 heads)
- anconeus
- brachioradialis
- extensor carpi radialis longus & brevis (latter originates ≈ at terminal branch)
- supinator (originates near the terminal branch)
- continues into forearm as **posterior interosseous nerve** (C7, C8)
  - extensor carpi ulnaris
  - extensor digitorum
  - extensor digiti minimi
  - extensor pollicis brevis & longus
  - abductor pollicis longus
  - extensor indicus

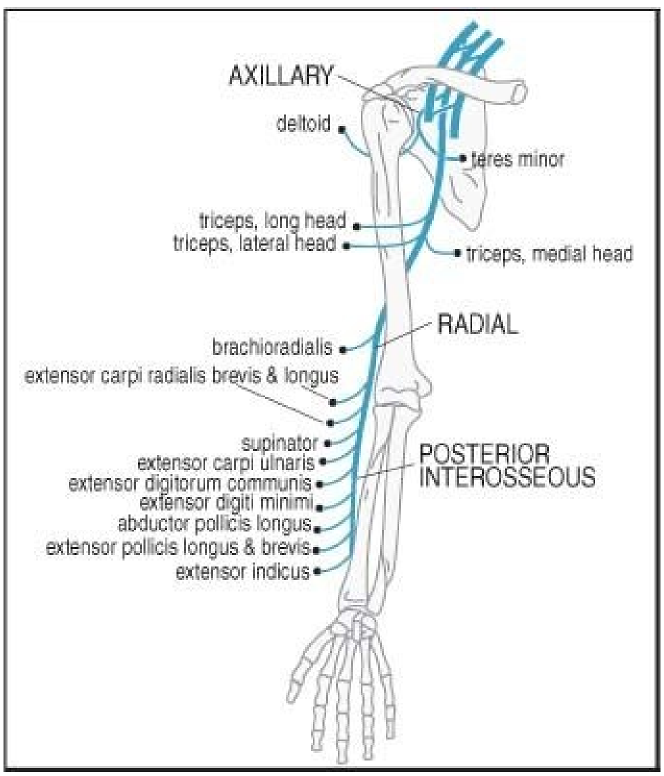

Figure 24-2 Muscles of the radial and axillary nerves

Axillary nerve (C5, C6)

See *Figure 24-2*.

- teres minor
- deltoid

Median nerve (C5-T1)[A]

A. also, *see page 792* for Martin-Gruber anastomosis

See *Figure 24-3*.

1. nothing in arm
2. all forearm pronators and flexors except the two supplied by ulnar nerve
   - pronator teres
   - flexor carpi radialis
   - palmaris longus
   - flexor digitorum superficialis
3. in the hand ⇒ only the "**LOAF** muscles"
   - **L** umbricals 1 & 2
   - **O** pponens pollicis
   - **A** bductor pollicis brevis
   - **F** lexor pollicis brevis (C8, T1)

- branch at or just distal to elbow **anterior interosseous nerve** (purely motor)

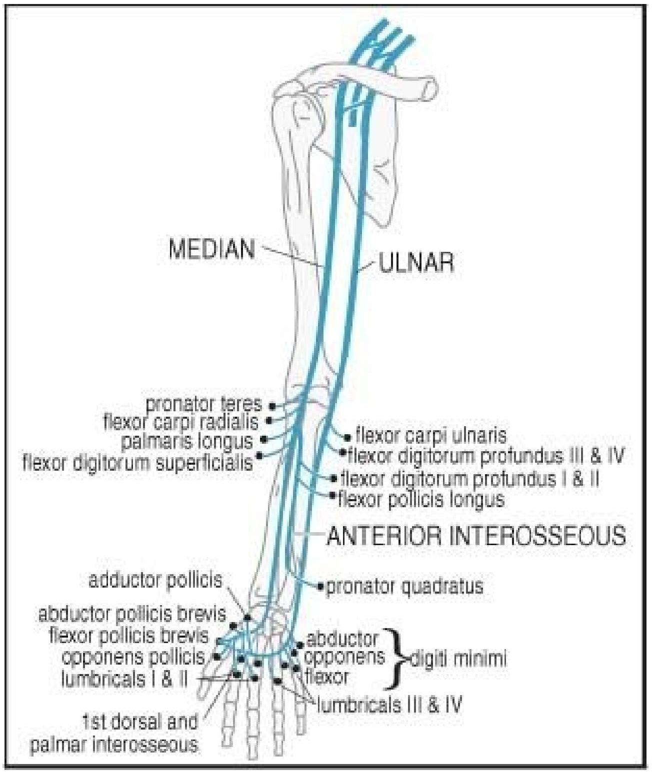

Figure 24-3 Muscles of the median and ulnar nerves

- flexor digitorum profundus I & II
- flexor pollicis longus
  - pronator quadratus

Ulnar nerve (C8, T1)[A]

See *Figure 24-3*.

1. nothing in arm
2. only 2 muscles in forearm:
   - flexor carpi ulnaris
   - half of flexor digitorum profundus (parts III & IV)
3. all hand muscles excluding "LOAF" muscles (*see above*), viz.:
   - adductor pollicis
   - all interossei (4 dorsal & 3 palmar)
   - lumbricals 3 & 4
   - 3 hypothenar muscles: abductor, opponens & flexor digiti minimi
   - deep part of flexor pollicis brevis (by deep branch of ulnar nerve)
   - palmaris brevis (by the superficial branch of the ulnar nerve)

Musculocutaneous nerve (C5, C6)

Supplies arm flexors

- coracobrachialis
- biceps
- brachialis
- **lateral cutaneous nerve of the forearm** (terminal branch) supplies cutaneous sensation to radial aspect of forearm

Dorsal scapular nerve (C4, C5)

- rhomboids (major & minor)
- levator scapulae

Suprascapular nerve (C5, C6)

- supraspinatus
- infraspinatus

Subscapular nerve (C5-7)

- teres major
- subscapularis

Thoracodorsal nerve (C6, C7, C8)

- latissimus dorsi

Long thoracic nerve (C5-7)

Originates off of proximal nerve roots

- serratus anterior (holds scapula to chest wall): lesion → **winging of the scapula**[A] (to test: patient leans forward against wall with arms outstretched, scapula separates from posterior chest wall if the serratus anterior is not contracting)

A. this is classic winging of the scapula. A variant of winging can occur with loss of trapezius muscle (e.g. with accessory nerve injury), and typically manifests when the patient pushes forward with the elbow held at the side of the thorax

Anatomic variants

Martin-Gruber anastomosis[5]: Anastomosis between median and ulnar nerves in the forearm found in 16 of 70 (23%) cadavers, bilateral in 3 (19%). Pattern I (90%): 1 anastomotic branch, Pattern II (10%) had 2.

Classification based on the origin from the median nerve: Type a (47.3%) from the branch to the superficial forearm flexor muscles, Type b (10.6%) from the common trunk, and Type c (31.6%) from the anterior interosseous nerve. Pattern II was a duplication of Type c (10.5%). The anastomotic branch was undivided in 15 cases, and divided into two branches in four cases. The anastomosis took an oblique angle or arched course to the ulnar nerve and passed superficial to the ulnar artery in four cases, deep to it in six, and in nine cases it was related to the anterior ulnar recurrent artery[5].

Richie-Cannieu anastomosis: Motor connections from median to ulnar nerve at the palm. Found in 70% of patients.

24.3. Peripheral neuropathies

Definitions

peripheral neuropathy	(the term polyneuropathy is also sometimes used) diffuse lesions of peripheral nerves producing weakness, sensory disturbance, and/or reflex changes
mononeuropathy	a disorder of a single nerve, often due to trauma or entrapment
mononeuropathy multiplex	involvement of 2 or more nerves, usually due to a systemic abnormality (e.g. vasculitis, rheumatoid arthritis, DM…). Treatment is directed at the underlying disorder

A mnemonic for etiologies of peripheral neuropathies is “GRAND THERAPIST” (*see Table 24-8*). Diabetes, alcoholism, and Guillain-Barré (underscored in table) account for 90% of cases. Other etiologies include: arteritis/vasculitis, monoclonal gammopathy (*see page 799*), hepatitis C virus-associated cryoglobulinemia, acute idiopathic polyneuritis, Sjögren’s syndrome (disease).

Table 24-8 Mnemonic for etiologies of peripheral neuropathy

Guillain-Barré (*see page 66*)	**T**raumatic
Renal (uremic neuropathy -*see page*	**H**ereditary

800)	**E**ndocrine or **E**ntrapment
Alcoholism (*see below*)	**R**adiation
Nutritional (B_{12} deficiency…)	**A**myloid (*see page 800*) or **A**IDS (*see page 798*)
Diabetes (*see below*) or **D**rugs (*see page 797*)	**P**orphyria or **P**sychiatric or **P**araneoplastic (*see below*) or **P**seudoneuropathy (*see below*) or PMR (*see page 75*)
	Infectious/post-infectious (e.g. Hansen's disease)
	Sarcoidosis (neurosarcoidosis, *see page 71*) or "**S**ystemic"
	Toxins (including heavy metals, e.g lead toxicity (plum-bism), *see page 998*)

Clinical

Peripheral neuropathies can present as loss of sensation, pain, weakness, incoordination and difficulty ambulating.

Evaluation

Initial (generic) work-up for peripheral neuropathies of unknown etiology:

1. bloodwork: Hgb-A1C, TSH, ESR and vitamin B_{12}
2. EMG

Classification

1. inherited neuropathies
   A. **Charcot-Marie-Tooth (CMT)** (AKA peroneal muscular atrophy, AKA Hereditary Motor and Sensory Neuropathy **(HMSN)**): Up to 7 types, (the most common form is autosomal dominant, but X-linked recessive forms also exist). CMT Types 1 & 2 together make up the most common inherited disorder of peripheral nerves (up to 40/100,000). The most common forms involve demyelination. Progressive loss of motor (primarily distal LE) and, to a lesser degree, sensory function (predominantly proprioception and vibration), with atrophy in UEs & LEs. Earliest findings: pes cavus with hammer toes, foot drop and frequent ankle sprains. Patients are more susceptible to entrapment neuropathies due to underlying compromise of peripheral nerves. Patients with Type 1 usual maintain ability to ambulate, whereas Type 2 usually lose ambulation by their teenage years

   B. hereditary neuropathy with liability to pressure palsies **(HNPP)**: similar to CMT but due to focal areas of irregular thickening of myelin sheaths ("tomaculous" changes), mild trauma or pressure can produce nerve palsies that may last for months
2. acquired neuropathies: see sections below for details

A. acquired pure <u>sensory</u> neuropathies (in the absence of autonomic dysfunction) are rare. May be seen with pyridoxine therapy or paraneoplastic syndromes (*see below*)

B. entrapment neuropathies: *see page 804*

3. pseudoneuropathy

   A. **definition**: psychogenic somatoform disorders or malingering, reproducing the pains, paresthesias, hyperalgesia, weakness, and even objective findings such as changes in color and temperature which may mimic neuropathic symptoms[6]

CRITICAL ILLNESS POLYNEUROPATHY (CIP)

AKA neuropathy of critical illness, ICU neuropathy… For DDx, *see page 68* under *Guillain-Barré syndrome*.

Diagnostic criteria:

1. presence of sepsis, multi-organ failure, respiratory failure, or septic inflammatory response syndrome (SIRS)
2. difficulty weaning from ventilator or extremity weakness
3. EMG: ↓ amplitudes of compound muscle action potentials **(CMAP)** & SNAP
4. widespread muscle denervation potentials
5. normal or only mild increase in serum CPK levels

May occur in up to 70% of septic patients (not all are significantly symptomatic). Affects primarily distal muscles. Recovery occurs in weeks to months (faster than Guillain-Barré). Treatment is supportive. Complete recovery in 50%

PARANEOPLASTIC SYNDROMES AFFECTING THE NERVOUS SYSTEM

Occurs in < 1% of cancer patients. Peripheral <u>sensory</u> neuropathy of unknown etiology has been associated with cancer since its earliest description[7]. Therefore, in patients with **sensory neuropathy** of unknown etiology, occult neoplasms should be ruled out. If the work-up is negative, the patient should be followed since up to 35% of patients will be found to have cancer after a mean interval of 28 months 8.

ALCOHOL NEUROPATHY

Characteristically produces a diffuse sensory neuropathy, with absent achilles reflexes.

BRACHIAL PLEXUS NEUROPATHY[9] (918)

Differential diagnosis of etiologies of brachial plexopathy:

1. Pancoast syndrome or Pancoast tumor AKA superior sulcus tumor. Clinical: various combinations of pain in the shoulder radiating into the upper extremity in the ulnar nerve distribution from involvement of the lower brachial plexus, atrophy of hand muscles, Horner's syndrome (*see page 833*), UE edema. Etiologies:
   A. neoplasms:
      1. most common: bronchogenic cancer, usually non-small cell (NSCLC) (squamous cell or adenocarcinoma) arising in the pulmonary apex
      2. metastases
   B. infections
   C. inflammatory: granulomas, amyloid
2. (idiopathic) brachial plexitis: most commonly upper plexus or diffuse (*see below*)
3. cervical rib
4. viral
5. following radiation treatment: often diffuse (*see below*)
6. diabetes
7. vasculitis
8. inherited: dominant genetics
9. trauma (*see page 801*)

Evaluation: when the etiology is unclear, check CXR (with apical lordotic view), glucose, ESR and ANA. Idiopathic brachial plexitis will usually start to show some improvement by about 4 weeks. Obtain MRI through the plexus if no improvement by ≈ this time.

NEURALGIC AMYOTROPHY OF THE UPPER EXTREMITY

AKA idiopathic brachial plexus neuropathy AKA (paralytic) **brachial neuritis**, AKA brachial plexitis, AKA Parsonage-Turner syndrome[10], among others. Idiopathic. Not clearly infectious or inflammatory; allergic mechanism possible. Prognosis is generally good. Common patterns: single or multiple

mononeuropathy, plexopathy, or some combination. Demographics are shown in *Table 24-9*.

In a review of 99 cases[11]: predominant symptom is acute onset of intense pain, with weakness developing simultaneously or after a variable period (70% occur within 2 weeks of pain) usually as the pain lessened[10, 12]. Weakness never preceded pain, onset of weakness was sudden in 80%. Pain was usually constant, and described as “sharp”, “stabbing”, “throbbing” or “aching”. Arm movement exacerbated pain, and muscle soreness was noted in 15%. Pain lasted hours to several weeks. Paresthesias occurred in 35%. Pain usually lacked radicular features. When bilateral, weakness is usually asymmetric.

Exam

Weakness or paralysis in 96%, confined to shoulder girdle in 50%. In descending order of involvement: deltoid, spinati, serratus anterior, biceps brachii, and triceps. Winging of the scapula occurred in 20%. Sensory loss occurred in 60% of plexus lesions, of mixed variety (superficial cutaneous and proprioceptive). Sensory loss most common in outer surface of upper arm (circumflex nerve distribution) and radial aspect of forearm. Reflexes were variable.

Overall distribution judged to predominantly involve upper plexus in 56%, diffuse plexus in 38%, and lower in 6%.

Table 24-9 Neuralgic amyotrophy

incidence	1.64 per 100,000 population
male:female	2.4:1
age range at onset	3 mos - 75 years
prodrome	• ≈ 45% had viral prodrome (URI in 25%) • may follow vaccination
onset	rapid onset of pain or paralysis/paresis
initial symptom	pain in 95%
weakness	• 50% confined to shoulder girdle • 10% confined to a single peripheral nerve
sensory deficit	67%, usually axillary and antebrachial cutaneous
laterality	• 66% unilateral (right side 54%) • 34% bilateral
lab tests	normal

EMG/NCV

May help localize the portion of the plexus involved, and may detect subclinical involvement of the contralateral extremity. Must wait ≥ 3 weeks from onset for findings. Differentiating from cervical radiculopathy: SNAP should be normal in radiculopathy whereas some involvement usually occurs in plexitis. Cervical paraspinals will usually be normal in plexitis (except for very severe cases where there can be some retrograde involvement), and will be abnormal (fibrillations) in radiculopathy (except in cases where there has been enough time that significant recovery has occurred).

Outcome

Functional recovery is better in patients with primarily upper plexus involvement. After 1 year, 60% of upper plexus lesions were functioning normally, whereas none with lower involvement were (latter took 1.5-3 years). Rate of recovery estimated to be 36% within 1 year, 75% within 2, and 89% by 3 years. Recurrence was seen in only 5%. No evidence that steroids altered the course of the disease although it is still often prescribed in the acute phase.

RADIATION INDUCED BRACHIAL PLEXUS NEUROPATHY

Often follows external beam irradiation in the region of the axilla for breast carcinoma. Produces sensory loss with or without weakness. CT or MRI or biopsy may be needed to rule-out tumor invasion of the brachial plexus.

LUMBOSACRAL PLEXUS NEUROPATHY[13]

Analogous to idiopathic brachial plexitis (*see above*). It is controversial whether this actually exists in isolation without diabetes. Often starts with LE pain of abrupt onset, followed in days or a few weeks by weakness with or without muscle atrophy. Sensory symptoms are less prominent, and usually involve paresthesias. Objective sensory loss is only occasionally seen. There may be tenderness over the femoral nerve.

Differential diagnosis

May be confused with femoral neuropathy or L4 radiculopathy when quadriceps weakness and wasting occurs. Similarly, L5 radiculopathy or peroneal neuropathy may be erroneously suspected when foot drop is seen. Straight leg raising may occasionally be positive. Conspicuously absent are:

back pain, exacerbation of pain by Valsalva maneuver or back motion, and significant sensory involvement. For differential diagnosis of foot drop, *see page 1194*. For other causes of sciatica, *see page 1188*.

Etiologies

Other etiologies are similar to that for brachial plexus neuropathy (*see above*) except that under tumor, a pelvic mass should be considered (check prostate on rectal exam).

Evaluation

Evaluation is as for brachial plexus neuropathy (*see above*), except that instead of a brachial plexus MRI, a lumbar MRI and pelvic CT should be done to rule out masses.

EMG is key to diagnosis: evidence of patchy denervation (fibrillation potentials, and motor unit potentials that are either decreased in number or increased in amplitude or duration and polyphasic) involving at least 2 segmental levels with <u>sparing</u> of the paraspinal muscles is highly diagnostic (once diabetes, etc. have been ruled-out).

Recovery from pain precedes return of strength. Improvement is generally monophasic, slow (years), and incomplete.

DIABETIC NEUROPATHY

≈ 50% of patients with DM develop neuropathic symptoms or show slowing of nerve conduction velocities on electrodiagnostic testing. Neuropathy may sometimes be the initial manifestation of diabetes. Diabetic neuropathy is reduced by tight control of blood glucose[14]. Disagreement exists over the number of distinct clinical syndromes; there is probably a continuum[15] and they likely occur in various combinations. Some of the more readily identified syndromes include:

1. **primary sensory polyneuropathy**: symmetric, affecting feet and legs more than hands. Chronic, slowly-progressive. Often with accelerated loss of distal vibratory sense (normal loss with aging is ≈ 1% per year after age 40). Presents as pain, paresthesias, and dysesthesias. Soles of feet may be tender to pressure. Meralgia paresthetica (*see page 818*) may be first manifestation
2. autonomic neuropathy: involving bladder, bowel, and circulatory reflexes (resulting in orthostatic hypotension). May produce impotence, impaired

micturition, diarrhea, constipation, impaired pupillary light response

3. **diabetic plexus neuropathy** 16 or proximal neuropathy: possibly secondary to vascular injury to nerves (similar to a diabetic mononeuritis):
   A. one that occurs in patients > 50 years old with mild diabetes type II that is often confused with femoral neuropathy. Causes severe pain in the hip, anterior thigh, knee, and sometimes medial calf. Weakness of the quadriceps, iliopsoas, and occasionally thigh adductors. Loss of knee jerk. Possible sensory loss over medial thigh and lower leg. Pain usually improves in weeks, the weakness in months
   ★ B. **diabetic amyotrophy**: occurs in similar patient population often with recently diagnosed DM. Alternative names include[17]: **Bruns-Garland syndrome**, ischemic mononeuropathy multiplex…[18]. Abrupt onset of asymmetric pain (usually deep aching/burning with superimposed lancinating paroxysms, most severe at night) in back, hip, buttocks, thigh, or leg. Progressive weakness in proximal or proximal and distal muscles, often preceded by weight loss. Patellar reflexes are absent or reduced. Sensory loss is minimal. Proximal muscles (especially thigh) may atrophy. EMG findings consistent with demyelination invariably accompanied by axonal degeneration, with involvement of paraspinals and no evidence of myopathy. Symptoms may progress steadily or stepwise for weeks or even up to 18 months, and then gradually resolve. Opposite extremity may become involved during the course or may occur months or years later. Sural nerve biopsy may suggest demyelination
   C. diabetic proximal neuropathy **(DPN)**: fairly similar findings to diabetic amyotrophy except for subacute onset of symmetric LE involvement that usually start with weakness may be a variant[19]. *Table 24-10* (adapted[19]) compares DPN to diabetic amyotrophy and chronic inflammatory demyelinating polyradiculoneuropathy **(CIDP)**

TREATMENT

Treatment of Bruns-Garland syndrome is primarily expectant, although immunotherapy (steroids, immune globulin, or plasma exchange) may be considered in severe or progressive cases (efficacy is unproven)[19].

Table 24-10 Comparison of diabetic amyotrophy, diabetic proximal neuropathy (DPN), & CIDP

Description	Diabetic amyotrophy	DPN	CIDP
Onset	acute	subacute	gradual
Initial symptoms	asymmetric pain→ weakness	symmetric weakness	symmetric weakness
UE weakness	no	uncommon	yes
Sensory loss	minimal	minimal	moderate
Areflexia	LE	LE	generalized
CSF protein	variable	increased	increased
Axonal pathologic changes	common	typical	uncommon
Conduction slowing	patchy	patchy	diffuse
Prognosis	good	good	poor without treatment
Response to immunotherapy	unknown	possible	yes
Course	monophasic	monophasic	progressive

For sensory polyneuropathy, good control of blood sugar contributes to reduction of symptoms. Adjunctive agents that have been used include:

1. **mexiletine** (Mexitil®): start at 150 mg q 8 hrs, and titrate to symptoms to a maximum of 10 mg/kg/d
2. **amitriptyline** (Elavil®) and fluphenazine (Prolix-in®): ***Rx***: start with 25 mg amitriptyline PO q hs and 1 mg fluphenazine PO TID; and work up to 75 mg amitriptyline PO q hs[20] (≈ 100 mg qd amitriptyline alone may also be effective[21]). Usefulness has been challenged[22], but many studies do show benefit[21, 23]. **Side effects:** that may limit use include sedation, confusion, fatigue, malaise, hypomania, rash, urinary retention, and orthostatic hypotension
3. **desipramine** (Norpramin®): more selective blocker of norepinephrine reuptake (which seems more effective for this condition than serotonin reuptake blockers). Effectiveness at mean doses of 110 mg/day ≈ same as amitriptyline and therefore may be useful for patients unable to tolerate amitriptyline[21]. **Side effects:** include insomnia (may be minimized by AM dosing), orthostatic hypotension, rash, bundle branch block, tremor, pyrexia. **Supplied**: 10, 25, 50, 75, 100 & 150 mg tablets
4. **capsaicin** (Zostrix®): effective in some (see *Capsaicin*, on page 566)
5. **paroxetine** (Paxil®): a selective serotonin reuptake inhibitor **(SSRI)** antidepressant. ***Rx***: 20 mg PO q AM. If necessary, increase by 10 mg/d q

week up to a maximum of 50 mg/day (except in elderly, debilitated, or renal or hepatic failure where maximum is 40 mg/day). **Supplied**: 20 mg (scored) & 30 mg tablets

6. **gabapentin** (Neurontin®) doses of 1800-3600 mg/d produces at least moderate pain relief from painful diabetic neuropathy in 60% of patients[24] and was ≈ as efficacious as amitriptyline[25]. Dosage must be reduced with renal insufficiency. For details, *see page 416*
7. **pregabalin** (Lyrica®) ***Rx***: start with 50 mg TID and increase up to a maximum of 100 mg PO TID within 1 week in patients with creatinine clearance ≥ 60 ml/min (see *Eq 3-1*, page 46 to estimate). Dosage must be reduced with renal insufficiency. **Supplied**: 25, 50, 75, 100, 150, 200, 225, 300 mg capsules

DRUG INDUCED NEUROPATHY

Many drugs have been implicated as possible causes of peripheral neuropathy. Those that are better established or more notorious include:

1. thalidomide: neuropathy may occur with chronic use, and may be irreversible[26]
2. metronidazole (Flagyl®)
3. phenytoin (Dilantin®)
4. amitriptyline (Elavil®)
5. dapsone: a rare complication reported with use in nonleprosy patients is a reversible peripheral neuropathy that may be due to axonal degeneration, producing a Guillain-Barré-like syndrome (*see page 66* for Guillain-Barré syndrome)
6. nitrofurantoin (Macrodantin®): may additionally cause optic neuritis
7. cholesterol lowering drugs: e.g. lovastatin (Mevacor®), indapamide (Lozol®), gemfibrozil (Lopid®)
8. thallium: may produce tremors, leg pains, paresthesias in the hands and feet, polyneuritis in the LE, psychosis, delerium, seizures, encephalopathy
9. arsenic: may produce numbness, burning and tingling of the extremities
10. chemotherapy: cisplatin, vincristine…

FEMORAL NEUROPATHY

Manifests as:

1. motor deficits:
    A. wasting and weakness of the quadriceps femoris (knee extension)

B. weakness of iliopsoas (hip flexion): if present, indicates very proximal pathology (lumbar root or plexus lesion) as the branches to the iliopsoas arise just distal to the neural foramina
2. diminution of the patellar (knee jerk) reflex
3. sensory findings:
   A. sensory loss over the anterior thigh and medial calf
   B. pain in same distribution may occur
4. mechanical signs: positive femoral stretch test (*see page 444*)

Differential diagnosis:
1. L4 radiculopathy: L4 radiculopathy should not cause iliopsoas weakness (see *L4 involvement*, page 1190)
2. diabetic plexus neuropathy (see *Diabetic neuropathy* above)
3. (idiopathic) lumbosacral plexus neuropathy (*see above*)

Etiologies:
1. diabetes: the most frequent cause
2. femoral nerve entrapment: rare
   A. may occur secondary to inguinal hernia or may be injured by deep sutures placed during herniorrhaphy
   B. secondary to prolonged pelvic surgery from retractor compression (usually bilateral)
3. intraabdominal tumor
4. femoral arterial catheterization: see *Neuropathy after cardiac catheterization* below
5. retroperitoneal hematoma (e.g. in hemophiliac or on anticoagulants)
6. during surgery (*see page 800*)

AIDS NEUROPATHY

3.3% of patients with AIDS will develop peripheral nerve disorders[27] (whereas none who were just HIV positive developed neuropathy). The most common disorder is distal symmetric polyneuropathy **(DSP)**, usually consisting of vague numbness and tingling, and sometimes painful feet (although it may also be painless). There may be subtle reduction of light tough and vibratory sense. Other neuropathies include mononeuropathies (usually meralgia paresthetica, *see page 818*), mononeuropathy multiplex, or lumbar polyradiculopathy. Drugs used to treat HIV can also cause neuropathies (*see below*).

The DSP in AIDS patients is often associated with CMV infection, *Mycobacterium avium intracellulare* infection, or may be due to lymphomatous invasion of the nerve or lymphomatous meningitis. May demonstrate a mixed axonal demyelinating type of neuropathy on electrodiagnostic testing.

Neuropathies associated with drugs used to treat HIV:

1. nucleoside reverse transcriptase inhibitors
   A. zidovudine (Retrovir®) (formerly AZT)
   B. didanosine (ddI; Videx®): can cause a painful dose-related neuropathy[28]
   C. stavudine (d4T; Zerit®): can cause sensory neuropathy which usually improves when d4T is discontinued, and may not recur if restarted at lower dose[28]
   D. zalcitabine (ddC; Hivid®): dose-related neuropathy can be severe and persistent. More common in patients with DM or didanosine treatment[28]
2. protease inhibitors
   A. ritonavir (Norvir®): can cause peripheral paresthesias
   B. amprenavir (Agenerase®): can cause perioral paresthesias

NEUROPATHY ASSOCIATED WITH MONOCLONAL GAMMOPATHY

Monoclonal gammopathies include myeloma (*see page 740*), Waldenstrom's macroglobulinemia, and non-malignant entities such as monoclonal gammopathy of undetermined significance **(MGUS)**. Much effort has gone into determining which benign gammopathies are or are not likely to progress, and will not be addressed here.

≈ 10% of patients with neuropathy with no apparent etiology will be determined to have a monoclonal gammopathy (malignant or otherwise).

Etiologies:

1. antibodies directed primarily against oligosaccharides of peripheral nerves, e.g. myelin associated glycoprotein **(MAG)**, producing demyelinating neuropathy
2. cryoglobulins may damage vaso-nervorum (small blood vessels nourishing peripheral nerves)
3. in malignant gammopathies, tumor cells can invade the peripheral nerves (lymphomatosis)
4. amyloidosis: deposition of amyloid in peripheral nerves (*see page 800*)

5. thalidomide used to treat some myelomas may cause neuropathy (*see page 797*)

Treatment:

1. IgM monoclonal gammopathies: reduce the IgM antibody concentration
2. IgG or IgA monoclonal gammopathies:
   A. treatment for myeloma related neuropathy is directed at treating the myeloma
   B. solitary plasmacytoma: excision or XRT can improve the neuropathy

PERIOPERATIVE NEUROPATHIES

Also, see *Neuropathy after cardiac catheterization* below. Most often involves ulnar nerve or brachial plexus. In many cases, a nerve that is abnormal but asymptomatic may become symptomatic as a result of any of the following factors: stretch or compression of the nerve, generalized ischemia or metabolic derangement. The injury may be permanent or temporary. Occurs almost exclusively in adults[29].

1. **ulnar neuropathy**: controversial. Often blamed on external nerve compression or stretch as a result of malpositioning. Although this may be true in some cases, in one series this was a factor in only ≈ 17%[30]. Patient-related characteristics are shown in *Table 24-11*[31]. Many of these patients have abnormal contralateral nerve conduction, suggesting a possible predisposing condition[32]. Many patients do not complain of symptoms until > 48 hours post-op[31-33]. Risk may be reduced by padding the arm at, and especially distal to, the elbow, and avoiding flexion of the elbow (avoid > 110° flexion which tightens the cubital tunnel retinaculum) and by reducing the amount of time convalescing in the recumbent position[33]
2. **brachial plexus neuropathy**: may be mistaken for ulnar neuropathy. May be associated with:
   A. median sternotomy (most common with internal mammary dissection). Posterior sternal retraction displaces the upper ribs and may stretch or compress the C6 through T1 roots (major contributors to the ulnar nerve)
   B. head-down positions where the patient is stabilized with a shoulder brace. The brace should be placed over the acromioclavicular joint(s), and non-slip mattresses and flexion of the knees may be used as adjuncts[29]
   C. prone position (rare): especially with shoulder abduction and elbow

flexion with contralateral head rotation[29]

3. **median neuropathy**: perioperative median nerve injury may result from stretch of the nerve. Rare. Seems to occur primarily in middle-aged muscular males. Padding should be placed under the forearms and hands to maintain mild elbow flexion[29]
4. lower extremity neuropathies: most occur in patients undergoing procedures in the lithotomy position[29]. Frequency of involvement in a large series of patients undergoing procedures in the lithotomy position[34]: common peroneal 81%, sciatic 15%, and femoral 4%. Risk factors other than position: prolonged duration of procedure, extremely thin body habitus, and cigarette smoking in the preoperative period

Table 24-11 Patient-related characteristics in anesthesia-related ulnar neuropathy

male gender
obesity (body mass index ≥ 38)
prolonged post-op bed rest

A. common peroneal neuropathy: susceptible to injury in the posterior popliteal fossa where it wraps around the fibular head. May be compressed by leg holders, which should be padded in this area
B. femoral neuropathy: compression of the nerve by self-retaining abdominal wall retractor or rendering the nerve ischemic by occlusion of the external iliac artery[29]. Hemorrhage into the iliopsoas muscle may also compress the nerve. Cutaneous branches of the femoral nerve may be injured during labor and/or delivery[35] (most are transient)
C. sciatic neuropathy: stretch injuries may occur with hyperflexion of the hip and extension of the knee as may occur in the lithotomy position
D. meralgia paresthetica[36]: tends to occur bilaterally in young, slender males positioned prone, with operations lasting 6-10^{+} hours. Onset: 1-8 days postop. Spontaneous recovery typically occurs over an average of 5.8 months

Management

Once a neuropathy is detected, determine if it is sensory, motor, or both. Pure sensory neuropathies are more often temporary than motor[31], and expectant

management for ≈ 5 days is suggested (have the patient avoid postures or activities that may further injure the nerve). Neurologic consultation should be requested for all motor neuropathies and for sensory neuropathies persisting > 5 days[29] (EMG evaluation will not usually be helpful earlier than ≈ 3 weeks after onset).

OTHER NEUROPATHIES

Amyloid neuropathy

Amyloid is an insoluble extracellular protein aggregate that can be deposited in peripheral nerves. Amyloidosis occurs in a number of conditions, e.g. in ≈ 15% of patients with multiple myeloma (also, *see page 740*). The neuropathy predominantly produces a progressive autonomic neuropathy and symmetric dissociated sensory loss (reduced pain and temperature, preserved vibratory sense). There is usually less prominent motor involvement. May predispose to pressure injury of nerves (especially carpal tunnel syndrome, *see page 810* for laboratory tests).

Uremic neuropathy

Occurs in chronic renal failure. Early symptoms include calf cramps ("Charlie horses"), dysesthetic pain in feet (similar to painful diabetic neuropathy) and "restless legs". Achilles reflexes are lost. A stocking sensory loss is followed later by LE weakness that starts distally and ascends. The offending toxin is not known. Dialysis or renal transplantation relieves the symptoms.

Neuropathy after cardiac catheterization

In a series of ≈ 10,000 patients followed after femoral artery catheterization[37] (e.g. for coronary angiography or angioplasty), neuropathy occurred in 0.2% (with an estimated range in the literature up to ≈ 3%). Risk factors identified include: patients developing retroperitoneal hematomas or pseudoaneurysms after the procedure, procedures requiring larger introducer sheaths (e.g. angioplasty & stent placement > diagnostic catheterization), excessive anticoagulation (PTT > 90 for at least 12 hours).

Two groups of patients were identified and are shown in *Table 24-12*.

Excruciating pain after the catheterization procedure often preceded the

development or recognition of neuropathy.

Table 24-12 Neuropathy after cardiac catheterization (N = 9585)[37]

Catheterization complication	Neurologic complication
Group I (4 patients)	
groin hematoma or pseudoaneurysm	sensory neuropathy in all 4 cases • in distribution of medial & intermediate femoral cutaneous nerves → isolated sensory neuropathy (dysesthesia & sensory loss) of the anterior and medial thigh • no motor deficit
Group II (16 patients)	
large retroperitoneal hematoma	femoral neuropathy • sensory in all 16 cases: dysesthesia of the anterior/medial thigh & medial calf • motor in 13 cases: iliopsoas & quadriceps weakness
	obturator neuropathy in 4 cases • sensory: upper medial thigh • motor: obturator weakness
	lateral femoral cutaneous nerve → meralgia paresthetica

Treatment:

After considering available information, the recommendation is to repair pseudoaneurysms surgically, but to treat the neuropathy conservatively. A case could not be made that surgical drainage of hematoma reduced the risk of neuropathy. Weakness from femoral or obturator neuropathy was treated with inpatient rehabilitation.

Outcome:

Group I patients all had resolution in < 5 mos. In group II, 50% had complete resolution in 2 mos. 6 patients had persistent symptoms, 5 had mild femoral sensory neuropathy (1 of whom felt it was at least somewhat disabling), 1 had mild persistent quadriceps weakness and occasionally walks with a cane.

PERIPHERAL NERVE INJURIES

ANATOMY OF PERIPHERAL NERVES (*see Figure 24-4*)

Endoneurium surrounds myelinated and unmyelinated axons. These bundles are gathered into **fascicles** surrounded by **perineurium**. The **epineurium** encases the nerve trunk, containing fascicles separated by interfascicular epineurium or **mesoneurium**.

NERVE REGENERATION

Peripheral nerves regenerate ≈ 1 mm/day (about 1 inch/month). Divide this figure into distance that the nerve has to traverse (from knowledge of anatomy) for guide as to how long to wait before considering failure of therapy (either operative or non-operative). However, this rule may not be applicable to long distances (> ≈ 12 inches), and it may take longer to traverse regions of entrapment, scar or nerve injury. There may also be fibrosis of the muscle beyond salvage.

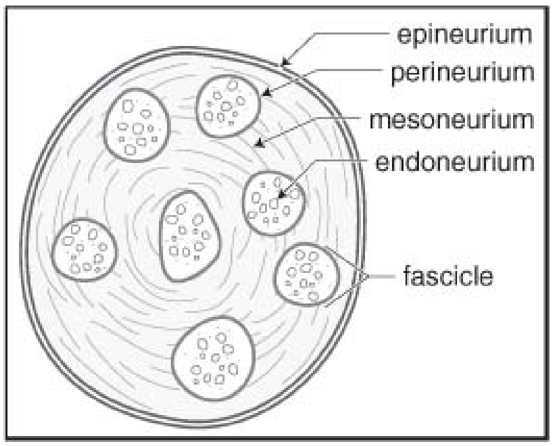

Figure 24-4 Anatomy of a peripheral nerve

PERIPHERAL NERVE INJURY CLASSIFICATION

There are numerous classification systems. The Seddon classification is an older 3-tiered system, The Sunderland system has 5 tiers, essentially dividing axonotmesis into 3 subgroups. Others have added a 6th category as shown in *Table 24-13*.

BRACHIAL PLEXUS INJURIES

Etiologies include:

1. penetrating trauma
2. traction (stretch injuries): more likely to affect the posterior and lateral cords than the medial cord and median nerve
3. first rib fractures
4. compression by hematoma

Initial exam seeks to differentiate preganglionic injuries (proximal to dorsal root ganglion) which cannot be repaired surgically, from postganglionic injuries. Clues to a **preganglionic injury** include:

1. Horner's syndrome: pre-ganglionic injury interrupts white rami communicantes
2. paralysis of serratus anterior (long thoracic nerve): produces winging of scapula
3. paralysis of rhomboids (dorsal scapular nerve)
4. early neuropathic pain suggests nerve root avulsion. MRI or myelogram will show pseudomeningoceles at the avulsed levels
5. EMG: requires ≥ 3 weeks from injury for some findings. Look for:
   A. denervation potentials in paraspinal muscles due to loss of neural input. The posterior ramus of the spinal nerve originates just distal to the dorsal root ganglion. Due to overlap, cannot localize to a specific segment
   B. normal sensory nerve action potential **(SNAP)**: preganglionic injuries leave the dorsal ganglion sensory cell body and the distal axon intact, so that normal SNAP can be recorded proximally even in an anesthetic region
6. pseudomeningocele on myelography or MRI: suggests nerve root avulsion (very proximal), however, 15% of pseudomeningoceles are not associated with avulsions, and 20% of avulsions do not have pseudomeningoceles[38, 39]

Table 24-13 Classification of peripheral nerve injury[*]

Seddon system	Sunderland system
Neuropraxia	**First-degree**
Features common to both systems Physiologic transection (nerve in continuity). Basement membrane intact. Compression or ischemia → local conduction block (impaired axonal transport). ★ No wallerian degeneration[†]. Motor involvement is typically > sensory. Autonomic function is preserved	
Recovers in hours to months; average is 6-8 weeks	Focal demyelination may occur. Recovery is usually complete in 2-3 weeks (not the "1 mm/day rule")
Axonotmesis	**Second-degree**
Features common to both systems Complete interruption of axons and myelin sheaths. Supporting structures (including endoneurium) intact. ★ Wallerian degeneration[†] occurs	
	Recovers at 1 mm/day as axon follows "tubule". Sometimes may only be diagnosed retrospectively. Recovery is poor in lesions requiring > 18 months to reach target muscle
	Third-degree
	Endoneurium disrupted, epineurium & perineurium intact. Nerve may not appear seriously damaged on gross inspection. Recovery may range

	from poor to complete and depends on degree of intrafascicular fibrosis
	Fourth-degree
	Interruption of all neural & supporting elements. Epineurium intact. Grossly: nerve is usually indurated & enlarged
Neurotmesis	**Fifth-degree**
Nerve completely severed or disorganized by scar tissue. Spontaneous regeneration impossible	Complete transection with loss of continuity
	Sixth-degree‡
	Mixed lesion. Combination of elements of first through fourth degree. There may be some preserved sensory fascicles (may produce a positive Tinel's sign)

* comparing and showing approximate equivalence of Seddon and Sunderland systems

† **wallerian degeneration** AKA orthograde degeneration, AKA secondary degeneration: degeneration of the axon distal to a focal lesion

‡ not part of original Sunderland system

(Duchene)-Erb's palsy

Upper brachial plexus injury (C5 & 6, some authors include C7) e.g. from forceful separation of humeral head from shoulder, commonly due to difficult parturition (*see below*) or motorcycle accident (downward force on shoulder can cause traumatic nerve root avulsion from the spinal cord). Paralysis of deltoid, biceps, rhomboids, brachioradialis, supra- & infraspinatus, and occasionally supinator. C7 involvement produces weak wrist extension.

Motor: arm hangs at side internally rotated & extended at elbow and flexed at the wrist ("**Bellhop's tip position**"). Hand motion is unaffected.

Klumpke's palsy

Injury to lower brachial plexus (C8 & T1, some authors include C7), from traction of abducted arm e.g. in catching onesulf during a fall from a height, or by Pancoast tumor (lung apex tumor - check CXR with apical lordotic view). Characteristic claw deformity (also seen with ulnar nerve injury) with weakness and wasting of small hand muscles. Possible Horner's syndrome if T1 involved.

Birth brachial plexus injury (BBPI)

Incidence is 0.3-2.0 per 1000 live births (0.1% in infants with birthweight <

4000 gm[40]). Rarely, a congenital case may be mistaken for BBPI[41]. Some contend that the plexus injury may occur when uterine contractions push the shoulder against the mother's pubic bone or with lowering of the shoulder with opposite inclination of the cervical spine[41].

Classification of BBPI injuries: Upper plexus injuries are most common, with about half having C5 & C6 injuries, and 25% involving C7 also[42]. Combined upper and lower lesions occur in ≈ 20%. Pure lower lesions (C7-T1) are rare, constituting only ≈ 2% and seen most commonly in breech deliveries. Lesions are bilateral in ≈ 4%. A 4-level scale of intensity is shown in *Table 24-14*[43].

Risk factors:

1. shoulder dystocia
2. high birth weight
3. primiparous mother
4. forceps[44] or vacuum assisted delivery
5. breech presentation[45]
6. prolonged labor
7. previous birth complicated by BBPI

Table 24-14 Birth brachial plexus injury

Group	Lesion	Manifestation	Spontaneous recovery rate
1	C5 or C6 roots or superior trunk	paralysis of shoulder abduction, elbow flexion & forearm supination. Finger flexion is norma	90%
2	above + involvement of C7 or medial trunk	above + paralysis of of finger extensors (but not flexors)	65%
3	above + finger flexors	essentially no hand movement. No Horner's syndrome	≈ < 50%
4	complete brachial plexus	flail arm + Horner's syndrome	0%
	"dominant C7" paralysis variant	selective loss of shoulder abduction & elbow extension	

Management of BBPI: Most surgeons observe all patients until age 3 months. Conservative surgeons may wait up to 9 months. More aggressive surgeons will explore the plexus at age 3 months if not anti-gravity in deltoid, biceps or triceps. In cases of proven avulsion (pseudomeningocele and EMG indicative of

a preganglionic injury), nerve transfers are a valid option at 3 months[46]. EMG may show signs of reinnervation, but the recovery may not be robust enough.

MANAGEMENT OF BRACHIAL PLEXUS INJURIES

1. most injuries show maximal deficit at onset. Progressive deficit is usually due to vascular injuries (pseudoaneurysm, A-V fistula, or expansile clot), these should be explored immediately
2. clean, sharp, relatively fresh lacerating injuries (usually iatrogenic, scalpel induced) should be explored acutely and repaired with tension-free end-to-end anastomoses within 24-48 hours (after that then ends will more edematous and therefore more difficult to suture)
3. penetrating non-missile injuries with severe or complete deficit should be explored as soon as the primary wound heals
4. gunshot wounds **(GSW)** to the brachial plexus: deficit is usually due to axonotmesis or neurotmesis (*see below*). Sometimes nerves may be divided. Nerves showing partial function usually recover spontaneously; those with complete dysfunction rarely do so. Surgery is of little benefit for discrete injuries to the lower trunk, medial cord, or C8/T1 roots. Most are managed conservatively for 2-5 months. Indications for surgery are shown in *Table 24-15*
5. traction injuries: incomplete postganglionic injuries tend to improve spontaneously. If recovery is not satisfactory, perform EMG at 4-5 months and explore at 6 months

Table 24-15 Indications for neurosurgical intervention in GSW to the brachial plexus[4]

1. complete loss in the distribution of at least one element
A. no improvement clinically or on EMG in 2-5 months
B. deficit in distribution that is responsive to surgery (e.g. C5, C6, C7, upper or middle trunk, lateral or posterior cords or their outflows)
C. injuries with loss only in lower elements are not operated
2. incomplete loss with failure to control pain medically
3. pseudoaneurysm, clot or fistula involving plexus
4. true causalgia requiring sympathectomy

6. neuromas in continuity: those that do not conduct a SNAP have complete internal disruption and require resection and grafting. Methods of repair:
   A. neurolysis:
      1. external neurolysis: most commonly performed in exploration. Value is questionable

2. internal neurolysis: splitting the nerve into fascicles. Not recommended unless a clear neuroma in continuity is found eccentric in the nerve that conducts SNAP

B. nerve grafting. Sural nerve is the most commonly used interposition graft following resection of neuroma in continuity

C. nerve transfers. Donor nerve options:
    1. spinal accessory nerve
    2. intercostal nerves to musculocutaneous nerve
    3. fascicles of the ulnar nerve for the median nerve (Oberlin procedure)
    4. anterior interosseous nerve to median nerve

24.3.1. Missile injuries of peripheral nerves

Most injuries from a single bullet are due to shock and cavitation from the missile causing axonotmesis or neurotmesis, and are not from direct nerve transection. Approximately 70% will recover with expectant management.

However, if there is a lack of improvement on serial examinations including electrodiagnostic studies, intervention should be undertaken by about 5-6 months to avoid further difficulties due to nerve fibrosis and muscle atrophy.

See *Table 24-15* for indications for surgery for missile injuries of the brachial plexus.

24.3.2. Entrapment neuropathies

Entrapment neuropathy is a peripheral nerve injury resulting from compression either by external forces or from nearby anatomic structures. Mechanism can vary from one or two significant compressive insults to many localized, repetitive mild compressions of a nerve. Certain nerves are particularly vulnerable at specific locations by virtue of being superficial, fixed in position, traversing a confined space, or in proximity to a joint. The most common symptom is pain (frequently at rest, more severe at night, often with retrograde radiation causing more proximal lesion to be suspected) with tenderness at the point of entrapment. May be associated with:

1. diabetes mellitus
2. hypothyroidism: due to glycogen deposition in Schwann cells
3. acromegaly

4. amyloidosis: primary or secondary (as in multiple myeloma)
5. carcinomatosis
6. polymyalgia rheumatica: *see page 77*
7. rheumatoid arthritis: 45% incidence of 1 or more entrapment neuropathies
8. gout

Mechanism of injury

Brief compression primarily affects myelinated fibers, and classically spares unmyelinated fibers (except in cases of *severe* acute compression). Acute compression compromises axoplasmic flow which can reduce membrane excitability. Chronic compression affects both myelinated and unmyelinated fibers and can produce segmental demyelination in the former, and if the insult persists, axolysis and wallerian degeneration will occur in both types. The issue of ischemia is more controversial[47]. Some contend that simultaneous venous stasis at the site of compression can produce ischemia which can lead to edema outside the axonal sheath which may further exacerbate the ischemia. Eventually, fibrosis, neuroma formation, and progressive neuropathy can occur.

OCCIPITAL NERVE ENTRAPMENT

Greater occipital nerve (nerve of Harnold) is a sensory branch of C2 (see *Figure 20-1*, page 551 for dermatome). Entrapment presents as **occipital neuralgia**: pain in occiput usually with a trigger point near the superior nuchal line. Pressure here reproduces pain radiating up along back of head towards vertex.

More common in women.

Differential diagnosis:

1. headache
    A. may be mimicked by migraine headache
    B. may be part of muscle contraction (tension) headache
2. myofascial pain[48]: the pain may be widely separated from the trigger point
3. vertebrobasilar disease including aneurysm and SAH
4. cervical spondylosis
5. pain from Chiari I malformation (*see page 233*)

Possible causes of entrapment:

1. trauma

A. direct trauma (including iatrogenic placement of suture through the nerve during surgical procedures, e.g. in closing a posterior fossa craniectomy)
B. following traumatic cervical extension[49] which may crush the C2 root and ganglion between the C1 arch and C2 lamina
C. fractures of the upper cervical spine (*see page 961* and *page 961*)

2. atlanto-axial subluxation **(AAS)** (e.g. in rheumatoid arthritis) or arthrosis
3. entrapment by hypertrophic C1-2 (epistrophic) ligament[50]
4. neuromas
5. arthritis of the C2-3 zygapophyseal joint

Treatment

> Σ For idiopathic occipital neuralgia: available evidence is from small, retrospective, case series studies and is insufficient to conclude that either local injection or surgery are effective. Nerve blocks with steroids and local anesthetics provide only temporary relief. Surgical procedures such as nerve root decompression or neurectomy may provide effective pain relief for some patients; however, patient-selection criteria for these procedures have not been defined, and recurrence is common.

In idiopathic cases with no neurologic deficit, the condition is usually self limited.

Non surgical treatment

1. greater occipital nerve block with local anesthetic and steroids (*see below*)
   A. may provide relief typically lasting ≈ 1 month[51]
   B. is no longer considered diagnostic because it is not sufficiently specific
2. physical therapy: massage and daily stretching exercises
3. TENS unit: provided ≥ 50% relief in 13 patients for up to 5 yrs[52]
4. oral anti-inflammatory agents
5. centrally acting pain medications: Neurontin, Paxil, Elavil…
6. botulinum toxin injection[53]: although this study had quite a few placebo responders

If these measures do not provide permanent relief in <u>disabling</u> cases, surgical treatment may be considered, although caution is advised by many due to poor results[48, 54]. Alcohol neurolysis may be tried. A collar is <u>not</u> indicated as it may irritate the condition.

Occipital nerve block: Inject trigger point(s) if one or more can be identified (there is usually a trigger point near the superior nuchal line). The nerve may also be blocked at the point where it emerges from the dorsal neck muscles.

If the pathology is more proximal (e.g. at C2 spinal ganglion), then block of the ganglion may be required. Technique[55] (done under fluoroscopy): shave hair below the mastoid process; prep with iodine; infiltrate with local; insert a 20 gauge spinal needle midway between C1 and C2, halfway between the midline and the lateral margin of the dorsal neck muscles. Aim rostrally, the final target is the midpoint of the C1-2 joint on AP fluoro, and almost but not touching the inferior articular process of C1. Infiltrate 1-3 ml of anesthetic and check for analgesia in the C2 distribution.

Surgical treatment

1. decompression of C2 nerve root if compressed between C1 and C2[50]
2. in cases of AAS, decompression and atlanto-axial fusion (*see* *page 183*) may work

Surgical treatment options for idiopathic occipital neuralgia:

1. peripheral occipital nerve procedures: these may not be effective for proximal compression of the C2 root or ganglion:
   A. occipital neurectomy (*see below*)
      1. peripheral avulsion of the nerve
      2. avulsion of the greater occipital nerve as it exits between the transverse process of C2 and the inferior oblique muscle
   B. alcohol injection of greater occipital nerve
2. occipital nerve stimulators
3. release of the nerve within the trapezius muscle. Immediate results: relief in 46%, improvement in 36%. Only 56% reported improvement at 14.5 mos[56]
4. intradural division of the C2 dorsal route via a posterior intradural approach
5. ganglionectomy

Occipital neurectomy: The occipital nerve usually pierces the cervical muscles ≈ 2.5 cm lateral to the midline, just below the inion. Palpation or doppler localization of the pulse of the accompanying greater occipital artery sometimes helps to locate the nerve. However, relief only occurs in ≈ 50%, and recurrence, usually within a year, is common.

MEDIAN NERVE ENTRAPMENT

The two most common sites of entrapment of the median nerve:

- at the wrist by transverse carpal ligament: carpal tunnel syndrome (*see below*)
- in upper forearm by pronator teres: pronator teres syndrome (*see page 809*)

ANATOMY

Contributing nerve roots: C5 through T1. The median nerve arises from the medial and lateral cords of the brachial plexus (see *Figure 24-1*, page 790), and descends the upper arm adjacent to the lateral side of the brachial artery. It crosses to the medial side of the artery at the level of the coracobrachialis. In the cubital fossa, the median nerve passes behind the lacertus fibrosus (bicipital aponeurosis) and enters the upper forearm between the two heads of the pronator teres and supplies this muscle.

Just beyond this point, it branches to form the purely motor anterior interosseous nerve which supplies all but 2 muscles of finger and wrist flexion. It descends adherent to deep surface of flexor digitorum superficialis **(FDS)**, lying on the flexor digitorum profundus. Near the wrist, it emerges from the lateral edge of FDS becoming more superficial, lying medial to the tendon of flexor carpi radialis, just lateral to and partially under the cover of the palmaris longus tendon. It passes under the transverse carpal ligament **(TCL)** through the **carpal tunnel** which also contains the tendons of the flexor digitorum profundus and superficialis deep to the nerve (9 tendons total, 2 to each finger, 1 to the thumb[57]). The motor branch arises deep to the TCL, but may anomalously pierce the TCL. It supplies the "LOAF muscles" (**L**umbricals 1 & 2, **O**pponens pollicis, and **A**bductor and **F**lexor pollicis brevis).

The TCL attaches medially to pisiform and hook of hamate, laterally to trapezium and tubercles of scaphoid. TCL is continuous proximally with fascia over FDS and antebrachial fascia, distally with the flexor retinaculum of the hand. The TCL extends distally into the palm to ≈ 3 cm beyond the distal wrist crease. The palmaris longus tendon, which is absent in 10% of population, partially attaches to the TCL.

Palmar cutaneous branch (PCB) of median nerve: arises from the radial aspect of the median nerve approximately 5.5 cm proximal to styloid process of the radius, underneath the cover of FDS of the middle finger. It crosses the wrist <u>above</u> the TCL to provide sensory innervation to the base of the thenar eminence (and is thus spared in carpal tunnel syndrome).

The sensory distribution of the <u>average</u> median nerve is shown in *Figure 24-5*.

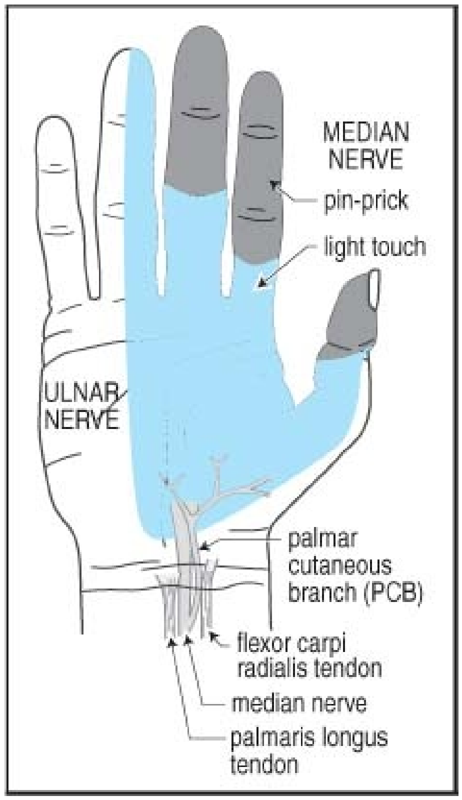

Figure 24-5 Sensory distribution of the median and ulnar nerves in the hand

INJURIES TO THE MAIN TRUNK OF THE MEDIAN NERVE

Above the elbow, the median nerve may rarely be compressed by Struther's ligament (*see below*). At the elbow and forearm, the median nerve may rarely be trapped at any of three sites: 1) lacertus fibrosus (bicipital aponeurosis)[58], 2) pronator teres, 3) sublimis bridge. Neuropathy may also result from direct or indirect trauma or external pressure ("**honeymoon paralysis**")[58]. Longstanding compression of the main trunk of the median nerve produces a "**benediction hand**" when trying to make a fist (index finger extended, middle finger partially flexed; due to weakness of flexor digitorum profundus I & II).

STRUTHER'S LIGAMENT

(Distinct from struthers *arcade* which is a normal finding, *see page 813*). The supracondylar process **(SCP)** is an anatomical variant located 5-7 cm above

medial epicondyle, present in 0.7-2.7% of population. Struther's ligament bridges the SCP to the medial epicondyle. The median nerve and brachial artery pass underneath, the ulnar nerve may also. Usually asymptomatic, but occasionally may cause typical median nerve syndrome.

PRONATOR (TERES) SYNDROME

From direct trauma or repeated pronation with tight hand-grip. Trapped where nerve dives between 2 heads of pronator teres. Causes vague aching and easy fatiguing of forearm muscles with weak grip and poorly localized paresthesias in index finger and thumb. Nocturnal exacerbation is absent. Pain in palm distinguishes this from carpal tunnel syndrome **(CTS)** since the median palmar cutaneous branch **(PCB)** exits before the TCL and is spared in CTS.

Treat with resting forearm. Surgical decompression indicated for cases that progress while on rest or when continued trauma is unavoidable.

ANTERIOR INTEROSSEOUS NEUROPATHY

Key concepts:

> - weakness of 3 muscles: FDP I & II, FPL, & pronator quadratus. No sensory loss
> - loss of flexion of the distal phalanges of the thumb and index finger (pinch sign)

The anterior interosseous nerve is a purely motor branch of the median nerve that arises in the upper forearm. Anterior interosseous neuropathy **(AIN)** produces no sensory loss and weakness of the 3 muscles supplied by the nerve:

1. flexor digitorum profundus **(FDP)** I & II: flexion of distal phalanx of digits 2 & 3
2. flexor pollicis longus **(FPL)**: flexion of distal phalanx of thumb
3. pronator quadratus (in the distal forearm): difficult to isolate clinically

Etiologies of AIN

Include: idiopathic, amyotrophy, ulna/radius fractures, penetrating injuries, forearm lacerations.

Clinical

Symptoms: Patients complain of difficulty grasping small objects between the

thumb and the index finger. Idiopathic cases may be preceded with forearm aching.

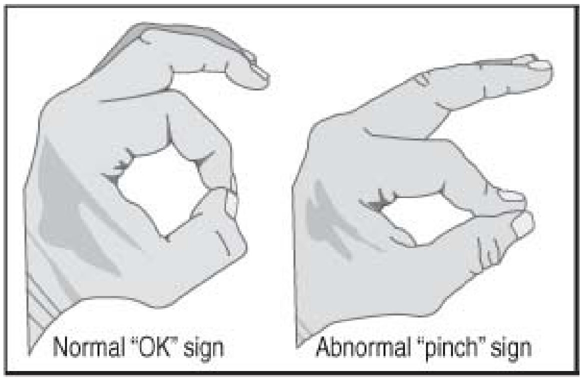

Figure 24-6 "Pinch sign" seen with AIN

Physical exam: Sensory: no sensory loss.

Strength: digits 1, 2 & 3 are examined individually. The proximal interphalangeal joints are stabilized by the examiner and the patient is asked to flex the DIP. With AIN, there is no significant flexion of the DIP.

Pinch sign: the patient attempts to forcefully pinch the tips of the index finger and thumb as in making an "OK" sign (*Figure 24-6*, left), with AIN the terminal phalanges extend and the pulps touch instead of the tips[59] (*Figure 24-6*, right).

Diagnosis

In addition to the physical exam, EMG may be helpful.

EMG: primarily assesses pronator quadratus & flexor pollicis longus (FDP I & II is difficult on EMG because it has dual innervation with the ulnar nerve innervated portion being more superficial than the median nerve innervated portion). Important to evaluate pronator teres (abnormalities suggest involvement more proximal than forearm).

Management

In the absence of an identifiable cause of nerve injury, expectant management is recommended for 8-12 weeks, following which exploration is indicated which may reveal a constricting band near the origin.

CARPAL TUNNEL SYNDROME

Key concepts:

- the most common compression neuropathy. Involves median nerve in the wrist
- symptoms: tingling in the hand, worse at night and with elevation of hands
- physical exam is not very sensitive:
  - sensory: decreased pinprick in digits 1-3 and the radial half of 4
  - sensitivity: Tinels (tapping on wrist) 60%, Phalens (flexion of wrist) 80%
- electrodiagnostics: sensory latency @ wrist **> 3.7 ms** is the most sensitive test
- treatment:
  - mild cases: nonsurgical treatment (NSAIDs, neutral position splint…)
  - severe cases (neurologic deficits, duration > 1 year): surgical neurolysis of the median nerve at the wrist has 70% satisfaction rate

Carpal tunnel syndrome **(CTS)** is the most common entrapment neuropathy in the upper extremity. The median nerve is compressed within its course through the carpal tunnel just distal to the wrist crease. *Table 24-16* shows the effect of pressure within the carpal tunnel.

Usually occurs in middle aged patients. Ratio of female:male = 4:1. It is bilateral in over 50% of cases, but is usually worse in the dominant hand.

Table 24-16 Pressure within carpal tunnel

Pressure (mm Hg)	Description
< 20	normal
20-30	venular flow retarded
30	axonal transport impaired
40	sensory & motor dysfunction
60-80	blood flow ceases

Common etiologies[60]

In most cases, no specific etiology can be identified. CTS is very common in the geriatric population without any additional risk factors. The following etiologies tend to be more common in younger patients:

1. "classic" CTS: chronic time course, usually over a period of months to years
   A. trauma: often job-related (may also be associated with avocations)

1. repetitive movements of hand or wrist
2. repeated forceful grasping or pinching of tools or other objects
3. awkward positions of hand and/or wrist, including wrist extension, ulnar deviation, or especially forced wrist flexion
4. direct pressure over carpal tunnel
5. use of vibrating hand tools

B. systemic conditions: in addition to systemic causes listed for entrapment neuropathies on page 804 (especially rheumatoid arthritis, diabetes), also consider:
1. obesity
2. local trauma
3. pregnancy: 54% remained symptomatic 1 year post-partum, and patients with onset early in pregnancy were less likely to improve[61]
4. mucopolysaccharidosis V
5. tuberculous tenosynovitis
6. multiple myeloma (amyloid deposition in flexor retinaculum) *see page 740*

C. patients with A-V dialysis shunts in the forearm have an increased incidence of CTS, possibly on an ischemic basis (steal and/or venous stasis) or possibly from the underlying renal disorder

2. "acute" CTS: an uncommon condition where the symptoms of CTS appear suddenly and severely, usually following some type of exertion or trauma. Etiologies:
   A. median artery thrombosis: < 10% of individuals have a persistent median artery
   B. hemorrhage or hematoma in the transverse carpal ligament

SIGNS AND SYMPTOMS

The physical exam for CTS is fairly insensitive. Signs and symptoms may include:

1. dysesthesias:
   A. characteristically patients are awakened at night by a painful numbness in the hand that often subjectively feels like a loss of circulation of blood. They often seek relief by: shaking or dangling or swinging the hand, opening and closing or rubbing the fingers, running hot or cold water over the hand, or pacing the floor. It may radiate up the arm, occasionally as far as shoulder

B. daytime activities that characteristically elicit symptoms usually involve prolonged hand elevation: holding a book or newspaper to read, driving a car, holding a telephone receiver, brushing the hair

C. distribution of symptoms:
   1. on palmar side in radial 3.5 fingers (palmar side of thumb, index finger, middle finger, and radial half of ring finger)
   2. dorsal side of these same fingers distal to the PIP joint
   3. radial half of palm
   4. subjective involvement of little finger occurs not infrequently

2. weakness of hand, especially grip. May be associated with thenar atrophy (late change, severe atrophy is seldom seen with current awareness of CTS by most physicians). An occasional patient may present with severe atrophy and no history of pain
3. clumsiness of the hand or difficulty with fine motor skills: due mostly to numbness more than a motor deficit. Often presents as difficulties buttoning buttons…
4. hypesthesia in median nerve sensory distribution: usually best appreciated in finger tips, loss of 2-point discrimination may be more sensitive test
5. **Phalen's test**: 30-60 secs of complete wrist flexion exaggerates or reproduces pain or tingling. Positive in 80% of cases[62]
6. **Tinel's sign** at the wrist: paresthesias or pain in median nerve distribution produced by gently percussing over the carpal tunnel. Positive in 60% of cases. May also be present in other conditions. Reverse Tinel's sign: produces symptoms radiating up the forearm for variable distance
7. ischemic testing: place blood pressure cuff proximal to wrist, inflation **x** 30-60 seconds may reproduce CTS pain

Differential diagnosis

Differential diagnosis includes (modified[63]):

1. cervical radiculopathy: coexists in 70% of patients with either median or ulnar neuropathy (C6 radiculopathy may mimic CTS). Usually relieved by rest, and exacerbated by neck movement. Sensory impairment has dermatomal distribution. It has been postulated that cervical nerve root compression may interrupt axoplasmic flow and predispose the nerve to compressive injury distally (the term **double-crush syndrome** was coined to describe this[64]), and although this has been challenged[65] it has not been disproven

2. thoracic outlet syndrome: loss of bulk in hand muscles other than thenar. Sensory impairment in ulnar side of hand and forearm (*see page 822*)
3. pronator teres syndrome: more prominent palmar pain than with CTS (median palmar cutaneous branch does not pass through carpal tunnel, *see page 807*)
4. **de Quervain's syndrome**: tenosynovitis of the abductor pollicis longus and extensor pollicis brevis tendons often caused by repetitive hand movements. Results in pain and tenderness in the wrist near the thumb. Onset in 25% of cases is during pregnancy, and many in 1st postpartum year. Usually responds to wrist splints and/or steroid injections. NCVs should be normal. Finkelstein's test: the thumb is passively abducted while thumb abductors are palpated, positive if this aggravates the pain[66]
5. reflex sympathetic dystrophy: may respond to sympathetic block (*see page 216*)
6. tenosynovitis of any of the flexor ligaments: may occasionally be due to TB or fungus. Usually a long, indolent course. Fluid accumulation may be present

DIAGNOSTIC TESTS

Electrodiagnostics

Electromyogram **(EMG)** and nerve conduction velocities **(NCV)**: may help confirm the diagnosis of CTS and distinguish it from cervical root abnormalities and from tendonitis.

NCV: it has been said the NCV can be normal in 15-25% of cases of CTS[A]. Sensory latencies are more sensitive than motor.

A. NB: normal sensory electrodiagnostics effectively rules-out CTS; great reservation should be exercised in considering operating on CTS with normal sensory NCV and amplitude

Normal findings are shown in *Table 24-17*. Abnormal values also listed are a rough guide, but the degree of latency prolongation does not reliably correlate with the severity of symptoms, ∴ grading should not be based on this alone. More validated definitions:

- mild: abnormal midplamar median velocity compared to radial or ulnar nerve

• moderate: prolonged antidromic or prolonged motor latency with amplitude loss
• severe: loss of motor axons on needle exam (EMG)

Table 24-17 Distal conduction latencies through carpal tunnel*

Degree of involvement†	Sensory latency‡ (mSec)	Sensory amplitude (μV)	Motor latency§ (mSec)	Motor amplitude (mV)
normal	< 3.7	> 25	< 4.5	> 4
mild†	3.7-4.0		4.4-6.9	
moderate†	4.1-5.0		7.0-9.9	
severe†	> 5 or unobtainable		> 10	

* assumes normal proximal NCV
† severity does not reliably correlate with latency (*see text*)
‡ to index finger
§ to abductor pollicis brevis

In uncertain cases, compare median nerve sensory conduction velocity to that of the ulnar nerve (or radial nerve): normal median nerve should be at least 4 m/sec faster than the ulnar, reversal of this pattern suggests median nerve injury. Alternatively, the sensory latencies for the *palmar* median and ulnar nerves can be compared; the median nerve latency should not be ≥ 0.3 mS longer than the ulnar.

EMG: normal in up to 31% of cases of CTS. In advanced CTS, it may show increased polyphasicity, positive waves, fibrillation potentials, and decreased motor unit numbers on maximal voluntary thenar muscle contraction. EMG may detect cervical radiculopathy if motor involvement is present.

With severe "end stage" CTS, sensory and motor potentials may not be recordable, and EMG is not helpful in localizing (i.e. differentiating CTS from other etiologies).

Laboratory tests

Recommended in cases where etiology is unclear (e.g. young individual with no history of repetitive hand use).

1. thyroid hormone levels (T_4 (total or free) & TSH): to R/O myxedema
2. CBC: anemia is common in multiple myeloma, also to R/O amyloidosis
3. electrolytes:
   A. to R/O chronic renal failure that could cause uremic neuropathy

B. blood glucose: R/O diabetes

4. in cases suspicious for multiple myeloma: (*see page 741* for full details)
   A. 24 hour urine for kappa Bence-Jones protein
   B. bloodwork: serum protein electrophoresis **(SPEP)** and immune electrophoresis **(IEP)** (looking for IgG kappa band)
   C. skeletal radiologic survey
   D. anemia is common on the CBC

Imaging studies

Not routinely done unless a mass lesion is suspected.

Wrist MRI: very sensitive. Findings with CTS include: flattening or swelling of the nerve, palmar bowing of the flexor retinaculum. May also demonstrate ganglion cysts, lipomas… Enhancement may occur with hypervascular edema.

Diagnostic ultrasound: faster and less expensive than MRI, and can assess blood-flow and changes with different wrist positions. 18 MHz probes may improve images.

NON-SURGICAL MANAGEMENT

Recommended for cases of recent onset, mild involvement, or where exacerbating phenomena are expected to be corrected[67 (p 1776)] (e.g. post-partum). 89% with severe CTS (constant numbness, or sensory loss or weakness/atrophy) had a recurrence within 1 year, compared to 60% with mild CTS (intermittent numbness and no sensory or motor deficits)[104]. Options include:

1. rest
2. medications: non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, and pyridoxine (vitamin B_6) have been studied with no evidence of efficacy[57]
3. treatment of associated conditions (e.g. hypothyroidism or DM) is appropriate, but there is no data as to whether this relieves CTS[57]
4. **neutral position splints**: alleviates symptoms in > 80% of patients[102] (usually within a few days) and reduces prolonged sensory latencies[103]. Relapse is common. A trial of at least 2-4 weeks is recommended
5. steroid injection: symptoms improve in > 75% of patients[57]. 33% relapse within 15 mos. Repeat injections are possible, but most clinicians limit to

3/year

A. use 10-25 mg hydrocortisone. Avoid local anesthetics (may mask symptoms of intraneural injection)
B. inject into carpal tunnel (deep to transverse carpal ligament) to ulnar side of palmaris longus to avoid median nerve (in patients without palmaris longus, inject in line with fourth digit)
C. median nerve injuries have been reported with this technique[68], primarily due to intraneural injection (all steroids are neurotoxic upon intrafascicular injection, and so are some of the carrier agents)
D. risk factors for recurrence: severe electrodiagnostic abnormalities, constant numbness, impaired sensation, & weakness or atrophy of thenar muscles[57]

SURGICAL TREATMENT

Indications: Surgical intervention is recommended for: constant numbness, symptoms > 1 year duration, sensory loss, or thenar weakness/atrophy[57]. Surgical treatment of cases due multiple myeloma is also effective.

The operation is commonly called a carpal tunnel release, AKA neurolysis of the median nerve at the wrist.

With bilateral CTS, in general one operates on the more painful hand first. However if the condition is severe in both hands (on EMG) and if it has progressed beyond the painful stage and is only causing weakness and/or numbness, it may be best to operate on the "better" hand first in order to try and maximize recovery of the median nerve at least on that side. Simultaneous bilateral procedures may also be done[69]. In severe cases, nerve recovery may not occur, it may be necessary to wait up to a year to tell.

Success rate:> 70% of patients report satisfaction with their surgical results[105], with 70-90% being free of nocturnal pain[105, 106].

Surgical techniques

A number of techniques are popular, including: incision through palm of hand, transverse incision through wrist crease (with or without a retinaculatome[70]), and endoscopic techniques (using single or dual incisions). The efficacies of the various approaches have not been compared in an adequately powered randomized study[57].

Transpalmar approach: (*see Figure 24-7*) Usually performed under local or regional anesthesia on outpatient basis. Magnification (operating loupes) are helpful.

Incision along imaginary line extending proximally from space between digits 3 and 4 (usually stay just to the ulnar side of the interthenar crease to avoid the PCB). The location of the median nerve may also be estimated by the palmaris longus tendon (stay slightly to ulnar side of tendon). Incision starts at distal wrist flexion crease, and the length depends on thickness of hand (it may extend as far distally as a line even with the crotch of the thumb). Optionally: curve ulnarward at proximal wrist flexion crease (to facilitate retraction).

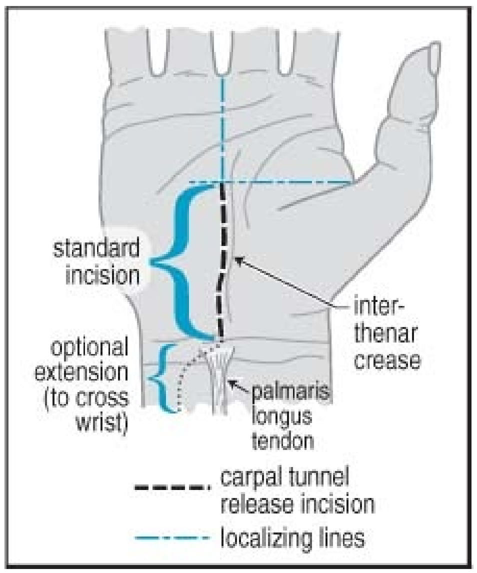

Figure 24-7 transpalmar incision for carpal tunnel syndrome

The median nerve is carefully approached through the TCL with progressively deepening incisions made with a 15 blade. All approaches to CTS surgery require complete division of TCL in the wrist. If tendons of the flexor digitorum superficialis are encountered, you need to look radially (towards the thumb) to find the nerve. In selected cases, the epineurium may be opened; however, internal neurolysis probably does more harm than good and should be avoided.

Close with absorbable 4-0 inverted sutures. Approximate skin edges with 4-0 nylon running or interrupted vertical mattress. Pad palm with several fluffs (opened dressing sponge). Cover with Kerlix®.

Post-op: wrap hand with thumb exposed. Wrist elevation and rest is recommended for several days. Analgesics for mild-to-moderate pain (e.g. acetaminophen with codeine) for 3-4 days. Sutures are removed at 7-10 days. No

heavy work with hand for 2-3 weeks.

<u>Complications</u> of carpal tunnel surgery[71]

1. pain due to neuroma formation following transection of **palmar cutaneous branch (PCB)** of the median nerve
   - branches of PCB may cross interthenar crease
   - avoid by: using magnification, <u>avoiding transverse wrist incision</u>, and making incision slightly to ulnar side of interthenar crease
   - treated by ligating this branch where it originates from median nerve in forearm (results in small area of numbness at base of thenar eminence)
2. neuroma of dorsal sensory branch of radial nerve
   - caused by extending incision proximally and radially
   - may be treated by neurolysis of neuroma
3. injury to **recurrent thenar (motor) branch** of median nerve
   - anomaly may cause nerve to lie above or to pierce TCL
   - avoided by: staying to <u>ulnar side</u> of midline
4. direct injury to median nerve
5. volar displacement and entrapment of median nerve in healing edges of TCL
6. hypertrophic scar causing compression of median nerve
   - usually caused by incision crossing wrist perpendicular to flexion crease
   - avoid by not crossing flexion crease, or in cases where necessary cross wrist obliquely at 45° angle directed toward ulnar side[71] (see optional extension line in *Figure 24-7*)
7. failure to improve symptoms
   - incorrect diagnosis: if EMG or NCV not done pre-op, they should be done after surgical failure (to R/O e.g. cervical root involvement (look for posterior myotome involvement), or generalized peripheral neuropathy)
   - incomplete transection of TCL: the most common cause for failure if diagnosis is correct (also possibility of accessory ligament or fascial band proximal to TCL). When this is identified on re-exploration, 75% of patients will be cured or improved after division is completed
8. joint stiffness
   - caused by excessively long immobilization of wrist and fingers
9. injury to superficial palmar arch (arterial): usually results from “blind” distal division of TCL
10. bowstringing of flexor tendons

11. **complex regional pain syndrome** AKA reflex sympathetic dystrophy: exact incidence is unknown, reported in 4 of 132 patients in one series (probably too high, most surgeons will see only one or two cases in their career). Treatment with IV phentolamine has been suggested, but most cases are self limited after ≈ 2 weeks
12. infection: usually causes exquisite tenderness
13. hematoma: also usually quite painful and tender

ULNAR NERVE ENTRAPMENT

Ulnar nerve has components of C7, C8 and T1 nerve roots. Even though this is the second most prevalent entrapment neuropathy after CTS, it is still relatively uncommon. Four potential sites of compression:

1. above elbow: possibly by the arcade of Struthers
2. at the elbow: retroepicondylar groove ("ulnar groove"): between the medial epicondyle and the olecranon process. Compression by fascia or by dynamic compression or repetitive trauma (*see page 813*)
3. forearm: just distal to the ulnar groove, under the aponeurosis between the heads of the flexor carpi ulnaris **(FCU)**
4. wrist: Guyon's canal

Motor findings include:

1. wasting of the interossei may occur, and is most evident in the first dorsal interosseous (in the thumb web space)
2. **Wartenberg's sign**: one of the earliest findings of ulnar nerve entrapment (abducted little finger due to weakness of the third palmar interosseous muscle)
3. **Froment's prehensile thumb sign**: grasping a sheet of paper between thumb and the extended index finger results in extension of the proximal phalanx of the thumb and flexion of the distal phalanx as a result of substituting flexor pollicis longus (innervated by anterior interosseous nerve) for the weak adductor pollicis[72] (p 18)
4. **claw deformity** of the hand (**main en griffe**): in severe ulnar nerve injuries on attempted finger extension (some have called this "benediction hand", which differs from that with the same name in median nerve injury where the named sign occurs on trying to make a fist - *see page 807*). Fingers 4 and 5 and to a lesser extent 3 are hyperextended at the MCP joints (extensor digitorum is unopposed by interossei and "ulnar"

lumbricals III & IV) and flexed at the interphalyngeal joints (due to pull of long flexor muscles). NB: C8 radiculopathy can also cause benediction sign[73])

INJURY ABOVE ELBOW

May occur with injury to the medial cord of the brachial plexus.

In the upper arm, the ulnar nerve descends anterior to the medial head of triceps; in 70% of people it passes under **arcade of Struthers** (distinct from Struther's ligament = *see page 807*) a flat, thin, aponeurotic band. This is not normally a point of entrapment, but may cause kinking after ulnar nerve transposition if not adequately divided[67 (p 1781)].

ENTRAPMENT AT ELBOW

Entrapment at or just distal to the elbow produces the **cubital tunnel syndrome**[A]. AKA **tardy ulnar palsy** because initial case reports occurred 12 or more years following injury at the elbow, with the majority commencing > 10 years following the original injury. The elbow is the most vulnerable point of ulnar nerve: here the nerve is superficial, fixed, and crosses a joint. Most cases are idiopathic, although there may be a history of elbow fracture (especially lateral condyle of the humerus, with associated cubitus valgus deformity), dislocation, arthritis, or repeated minor trauma. The aponeurotic arch extending over the ulnar groove and attaching on the medial epicondyle may become thickened and can compress the nerve, especially with elbow flexion[74 (p 884)]. The ulnar nerve may also be injured during anesthesia[75] (*see page 799*).

A. technically, the cubital tunnel is formed by the fibrous arch between the two heads of the FCU[74 (p 877)], the proximal entrance to which is just distal to the retrocondylar groove. However, common vernacular usually includes entrapment within the groove itself as being "cubital tunnel syndrome"

Table 24-18 McGowan classification of ulnar nerve injury

Grade	Description
1	purely subjective symptoms & mild hypesthesia
2	sensory loss & weakness of intrinsic hand muscles ± slight wasting
3	severe sensorimotor deficit

PRESENTATION

Typically presents with discomfort (pain, numbness and/or tingling) in little finger and ulnar half of ring finger, elbow pain, and hand weakness. Early symptoms may be purely motor (see *Froment's sign* and *claw deformity* above) - unlike the median nerve where sensory involvement is almost always present. Symptoms may be exacerbated by the cold, and are often somewhat vague and may be described as a loss of finger coordination or clumsiness. Cramping and easy fatiguing of the ulnar innervated muscles of the hand may occur. Pain may not be a significant feature, but if present tends to be aching in nature along the ulnar aspect of the elbow or forearm. Atrophy of interossei is common.

The ulnar nerve is usually tender and may be palpably enlarged in the ulnar groove.

Grading: the McGowan classification[76] is shown in *Table 24-18*.

EVALUATION

Electrodiagnostic studies

Sensory tests are not localizing for ulnar neuropathy (in contradistinction to median nerve/carpal tunnel), the *motor component* of the exam for the ulnar nerve is more useful for localization of the site of entrapment.

Summary of electrodiagnostic criteria for ulnar neuropathy at the elbow (not all need to be present)[77, 78]:

1. absolute motor nerve conduction velocity **(NCV)** < 50 m/sec from below elbow **(BE)** to above elbow **(AE)**
2. drop of NCV > 10 m/sec comparing BE to wrist segment to the AE to BE segment
3. amplitude of compound motor action potential **(CMAP)** normally decreases with distance, but a drop > 20% from BE to AE is abnormal (in the absence of anomalous innervation, e.g. Martin-Gruber anastomosis - *see page 792*)
4. EMG needle exam: not required. Can be normal in cases of neuropraxia (axonal loss causes abnormalities). It may be performed depending on results of above NCVs:
   A. gauges severity: severe involvement show signs of axonal loss such as fibrillation potentials, positive waves or giant waves
   B. helps differentiate ulnar neuropathy from cervical radiculopathy or brachial plexopathy. Check ulnar nerve innervated muscles including:

the first dorsal interosseous (FDI) should routinely be tested, abductor digiti quinti/minimi (ADQ), FDP to ring or little finger, FCU. If ulnar innervated muscles are abnormal, then check non-ulnar innervated C8/medial cord/lower trunk muscles & cervical paraspinals (e.g. opponens pollicis)

Diagnostic ultrasound

Localizing ulnar nerve lesions with electrodiagnostic studies can be difficult. There has been a recent renewed interest in diagnostic ultrasound using high frequency (18 MHz) probes to help with localization, and also for identification of pathology, including nerve swelling, transection[79], and neuroma, that exceeds MRI in some aspects and at a lower cost and with faster acquisition time.

NON-SURGICAL TREATMENT

Avoid elbow trauma: patient education, an elbow pad may help. Results are often better when definite traumatic etiology can be identified and eliminated.

SURGICAL TREATMENT

Most operations utilize a "lazy omega" skin incision centered over the medial epicondyle, extending at least ≈ 6 cm proximal and distal to elbow with the central "hump" directed anteriorly. The ulnar nerve is most constant and therefore most easily found immediately at the entrance to the ulnar groove. It may then be followed proximally and distally. Nerve branches that should be preserved include: posterior branches of the medial antebrachial cutaneous nerve (or else numbness or dysesthesias along medial forearm may occur) and branches to the flexor carpi ulnaris (which may branch early). Small articular branches at or proximal to the elbow joint can be preserved with simple decompression but may need to be sacrificed in transposition if they cannot be dissected far enough along the ulnar nerve. Internal neurolysis should be avoided as it may promote intraneural fibrosis.

The choice of one of the options below will determine subsequent steps.

Surgical options primarily consist of:

1. simple nerve decompression without transposition[80] (*see below*). Includes all of the following:
   A. at the elbow: division of the cubital tunnel retinaculum
   B. distal to the elbow: dividing the aponeurosis connecting the two heads of the flexor carpi ulnaris, some advocate resuturing the aponeurosis

underneath the nerve

   C. proximal to the elbow: dividing the medial intermuscular septum (between distal biceps and triceps muscles) and the arcade of Struthers (if present)
   D. preservation of the branch to the flexor carpi ulnaris and the dorsal cutaneous branch to the hand (arises 5 cm proximal to wrist)
2. nerve decompression and transposition (extent of surgery differs because degree of entrapment varies; all forms of transposition require fashioning a sling to retain the nerve in its new location). Transposition may be to:
   A. subcutaneous tissue: this leaves the nerve fairly superficial and vulnerable
   B. within the flexor carpi ulnaris muscle (intramuscular transposition): some contend this actually worsens the condition due to intramuscular fibrosis
   C. a submuscular position: see *Submuscular transposition* below
3. medial epicondylectomy. Usually combined with decompression. Normally reserved for patients with a bony deformity
4. sometimes excision of neuroma and possibly jump graft may be required

Submuscular transposition

Placement under pronator teres, within a groove fashioned in the flexor carpi ulnaris **(FCU)**. Usually requires general anesthesia (endotracheal or laryngeal mask airway).

Some key concepts[4 (p 247, 260-5), 81]:

1. the skin incision must extend at least ≈ 8 cm distal and proximal to the medial epicondyle to mobilize the nerve (spare the medial antecubital cutaneous nerve in the subcutaneous fatty tissue just distal to the elbow)
2. the nerve is mobilized, sparing branches to flexor carpi ulnaris **(FCU)** and the ulnar flexor profundi branch(es) (usually arise 2-4 cm distal to olecranon)
3. the medial intermuscular septum (between distal biceps and triceps muscles) must be cut in the distal arm to prevent the nerve from being kinked over it
4. the pronator teres muscle must be sectioned completely through just distal to the medial epicondyle
   A. start by undermining the muscle just distal to the medial epicondyle

B. a mosquito hemostat may be passed under the muscle to assist

C. the muscle is cut sharply, cautery is used to treat bleeding areas

5. a trough is cut in the volar aspect of the FCU to accommodate the nerve
6. after the pronator teres is reattached over the nerve, make sure that the nerve can slide back-and-forth easily under the muscle
7. test the elbow through a range of motion after the transposition to look for snapping of the medial portion of the triceps over the medial epicondyle[82]

Transposition vs. decompression

Σ For most cases, simple decompression is recommended over transposition. Possible exceptions include: bony deformity, nerve subluxation

Randomized studies have shown similar success but lower complication rate with simple decompression vs. transposition[83, 84]. Advantages of simple decompression include[85, 86]: shorter operation that can be done more easily under local anesthesia, avoidance of nerve kinking and muscular fibrosis around the transposed nerve, and preservation of cutaneous branches, ulnar branches, and nourishing blood vessels that are sometimes sacrificed with transposition, rendering portions of the nerve ischemic.

Arguments against simple decompression: Continued dynamic compression with elbow flexion, possible nerve subluxation (if present pre-op, simple decompression may make this worse)[A] and incomplete release of pressure points.

A. to avoid nerve subluxation and loss of vascular supply with simple decompression, avoid a 360° freeing of the nerve

Results with surgery

Not as good as with CTS, possibly due in part to the fact that patients tend to present much later. Overall, a good to excellent result is obtained in 60%, fair result in 25%, and a poor result (no improvement or worsening) in 15%[87] (p 2530). These results may be worse in patients with symptoms present > 1 year, with only 30% of these symptomatically improved in one series[80]. Lower success rate is also seen in older patients and those with certain medical

conditions (diabetes, alcoholism…). Pain and sensory changes respond better than muscle weakness and atrophy.

ENTRAPMENT IN THE FOREARM

Very rare. Just distal to the elbow, the ulnar nerve passes from the retroepicondylar groove to pass under the fascial band connecting the two heads of the flexor carpi ulnaris **(FCU)**, superficial to the flexor superficialis and pronator teres. Findings with entrapment in the forearm are similar to tardy ulnar nerve palsy (*see above*).

Surgical treatment consists of steps outlined for nerve *distal* to the elbow in ulnar nerve decompression (*see above*). A technique for locating the course of the ulnar nerve distal to the elbow: the surgeon takes the little finger of his/her own hand (using the hand contralateral to the patient's side that is being decompressed) and places the proximal phalanx in the ulnar groove aiming it toward the ulnar side of the wrist[4 (p 262)].

ENTRAPMENT IN THE WRIST OR HAND

At the wrist, the terminal ulnar nerve enters **Guyon's canal**, the roof of which is the palmar fascia and palmaris brevis, the floor is the flexor retinaculum of the palm and the pisohamate ligament.

Guyon's canal is <u>superficial</u> to the transverse carpal ligament (which overlies the carpal tunnel and compresses the median nerve in carpal tunnel syndrome).

The canal contains no tendons, only the ulnar nerve and artery. At the middle of the canal the nerve divides into deep and superficial branch. The superficial branch is mostly sensory (except for the branch to palmaris brevis), and supplies hypothenar eminence and ulnar half of ring finger. The deep (muscular) branch innervates hypothenar muscles, lumbricals 3 & 4, and all interossei. Occasionally the abductor digiti minimi branch arises from the main trunk or superficial branch.

Shea and McClain[88] divided lesions of the ulnar nerve in Guyon's canal into 3 types shown in *Table 24-19*. Injury to the distal motor branch can also occur in the palm and produces findings similar to a Type II injury.

Table 24-19 Types of ulnar nerve lesions in Guyon's canal

Type	Location of compression	Weakness	Sensory deficit
Type I	just proximal to or within Guyon's canal	all intrinsic hand muscles innervated by ulnar n.	palmar ulnar distribution*
Type II	along deep branch	muscles innervated by deep branch†	none
Type III	distal end of Guyon's canal	none	palmar ulnar distribution*

* palmar ulnar distribution: the hypothenar eminence and ulnar half of ring finger, both on the palmar surface only (the dorsum is innervated by the dorsal cutaneous nerve)

† depending on the location, may spare hypothenar muscles

Injury is most often due to a ganglion of the wrist[89], but also may be due to trauma (pneumatic drill, pliers, repetitively slamming a stapler, leaning on palm while riding bicycle). Symptoms are similar to those of ulnar nerve involvement at the elbow, except there will never be sensory loss in the dorsum of the hand in the ulnar nerve territory because the dorsal cutaneous branch leaves the nerve in the forearm 5-8 cm proximal to the wrist (sparing of flexor carpi ulnaris and flexor digitorum profundus III & IV is not helpful in localizing because these are so rarely involved even in proximal lesions). Electrodiagnostics are usually helpful in localizing the site of the lesion. Pain, when present, may be exacerbated by tapping over pisiform (Tinel's sign). It may also radiate up the forearm.

Surgical decompression may be indicated in refractory cases. To locate: find the ulnar artery, and the nerve is on the ulnar side of the artery. Controversial whether simple decompression vs. subcutaneous transposition is best, the outcome is similar but there may be more complications in the transposition group[83, 84] but studies are small.

RADIAL NERVE INJURIES[16] (1443-45)

Radial nerve arises from the posterior divisions of the 3 trunks of the brachial plexus. Receives contributions from C5 to C8. The nerve winds laterally along the spiral groove of the humerus where it is vulnerable to compression or injury from fracture.

Distinguish radial nerve injury from injury of posterior cord of brachial plexus by sparing of deltoid (axillary nerve) and latissimus dorsi (thoracodorsal nerve).

AXILLARY COMPRESSION

Less common than compression in mid-upper arm.

Etiologies: crutch misuse; poor arm position during (drunken) sleep.

Clinical: weakness of triceps and more distal muscles innervated by radial nerve.

MID-UPPER ARM COMPRESSION

Sites of compression: in spiral groove, at intermuscular septum, or just distal to this.

Etiologies:

1. "**Saturday night palsy**": improper positioning of arm in sleep (especially when drunk and therefore less likely to self-reposition in response to the accompanying discomfort, e.g. due to a bed-mate's head resting on the arm)
2. from positioning under general anesthesia
3. from callus due to old humeral fracture

Clinical: weakness of wrist extensors (**wrist drop**) and finger extensors. ★ Key: <u>triceps is normal</u> because takeoff of nerve to triceps is proximal to spiral groove. Involvement of distal nerve is variable, may include thumb extensor palsy and paresthesias in radial nerve distribution. Differential diagnosis: isolated wrist and finger extensor weakness can also occur in lead poisoning (usually bilateral, more common in adults).

FOREARM COMPRESSION

The radial nerve enters the anterior compartment of the arm just above the elbow. It gives off branches to brachialis, brachioradialis, and extensor carpi radialis **(ECR)** longus before dividing into the posterior interosseous nerve and the superficial radial nerve. The posterior interosseous nerve dives into the supinator muscle through a fibrous band known as the **arcade of Frohse** (*see page 791* for muscles supplied).

POSTERIOR INTEROSSEOUS NEUROPATHY

Posterior interosseous neuropathy ("**PIN**") may result from: lipomas, ganglia, fibromas, arthritis, entrapment at the arcade of Frohse (rare), and strenuous use of arm.

Clinical: marked extensor weakness of thumb and fingers (**finger drop**). Distinguished from radial nerve palsy by less wrist extensor weakness (no wrist drop) due to sparing of ECR brevis and longus (there will be radial deviation due to palsy of extensor carpi ulnaris). <u>No sensory loss</u> (c.f. what would occur with C8 radiculopathy).

Treatment: cases that do not respond to 4-8 weeks of expectant management should be explored, and any constrictions lysed (including arcade of Frohse).

Radial tunnel syndrome

AKA **supinator syndrome**. Controversial. The "radial tunnel" extends from just above the elbow to just distal to it, and is composed of different structures (muscles, fibrous bands…) depending on the level[90]. It contains the radial nerve and its two main branches (posterior interosseous and superficial radial nerves). Repeated forceful supination or pronation or inflammation of supinator muscle attachments (as in tennis elbow) may traumatize the nerve (sometimes by ECR brevis). Characteristic finding: pain in the region of the common extensor origin at the lateral epicondyle on resisted extension of the middle finger which tightens the ECR brevis. May be mistakenly diagnosed as resistant "tennis elbow" (lateral epicondylitis must be excluded). There may also be paresthesias in the distribution of the superficial radial nerve and local tenderness along the radial nerve anterior to the radial head. Even though the site of entrapment is similar to PIN, unlike PIN, there is usually no muscle weakness. Surgery: rarely required, consists of nerve decompression[90].

Injury in the hand

The distal cutaneous branches of the superficial radial nerve cross the extensor pollicis longus tendon, and can often be palpated at this point with the thumb in extension. Injury to the medial branch of this nerve occurs commonly e.g. with handcuff injuries, and causes a small area of sensory loss in the dorsal web-space of the thumb.

Axillary nerve injuries

Isolated neuropathy of the axillary nerve may occur in the following situations[91]:

1. shoulder dislocation: the nerve is tethered to the joint capsule[92]
2. sleeping in the prone position with the arms abducted above the head
3. compression from a thoracic harness
4. injection injury in the high posterior aspect of the shoulder
5. entrapment of the nerve in the quadrilateral space (bounded by the teres major and minor muscles, long head of triceps, and neck of humerus) which contains the axillary nerve and the posterior humeral circumflex artery. Arteriogram may show loss of filling of the artery with the arm

abducted and externally rotated

SUPRASCAPULAR NERVE

The suprascapular nerve is a mixed peripheral nerve arising from the superior trunk of the brachial plexus, with contributions from C5 & C6. There is often a history of shoulder trauma or frozen shoulder. Entrapment results in weakness & atrophy of infra-and supraspinatus (**IS** & **SS**) and deep, poorly localized (referred) shoulder pain (the sensory part of the nerve innervates the posterior joint capsule but has no cutaneous representation).

Etiologies:

1. nerve entrapment within the suprascapular notch beneath the **transverse scapular** (suprascapular) **ligament (TSL)**[93]
2. repetitive shoulder trauma: may be bilateral when the injury is from activities such as weight-lifting
3. ganglion or tumor[94] (MRI is the test of choice for imaging these)
4. paralabral cyst from labral tear (the tendon of the long head of the biceps attaches to the superior glenoid labrum; test of choice for labral tears is MR arthrography)

Differential diagnosis includes[93]:

1. pathology in or around shoulder joint
   A. rotator cuff injuries (distinction may be very difficult)
   B. adhesive capsulitis
   C. bicipital tenosynovitis
   D. arthritis
2. cases of Parsonage-Turner syndrome limited to the suprascapular nerve (see *Neuralgic amyotrophy*, page 794)
3. cervical radiculopathy (≈ C5) } NB: these two will also produce rhomboid and deltoid weakness and, usually, cutaneous sensory loss
4. upper brachial plexus lesion } NB: these two will also produce rhomboid and deltoid weakness and, usually, cutaneous sensory loss

Diagnosis requires temporary relief with nerve block, and EMG abnormalities of SS & IS (in rotator cuff tears, fibrillation potentials will be absent). Transient pain relief with a suprascapular nerve block helps verify the diagnosis[95].

Treatment:

In cases where a mass is not the underlying cause, initial treatment consists of resting the affected UE, PT (including gentle conditioning), NSAIDs, topical capsaicin cream, and sometimes corticosteroid injection.

Surgical treatment is indicated for documented cases that fail to improve with conservative treatment (PT, NSAIDs, steroid/local anesthetic injection…). Position: lateral decubitus. Incision: 2 cm above and parallel to the scapular spine (atrophy of SS facilitates this). Only the trapezius needs to be split along its fibers (caution re spinal accessory nerve). To locate suprascapular notch, follow omohyoid to where it attaches to scapula and palpate just lateral to this. The suprascapular artery and vein pass over the TSL and should be preserved. Elevate the TSL with a dull nerve hook and divide it (exposure of the nerve and/or resection of the bony notch are not necessary).

MERALGIA PARESTHETICA

Originally known as the **Bernhardt-Roth syndrome**, and sometimes called "swashbuckler's disease", meralgia paresthetica **(MP)** (Greek: *meros* - thigh, *algos* - pain) is a condition often caused by entrapment of the **lateral femoral cutaneous nerve (LFCN)** of the thigh, (a purely sensory branch with contributions from L2 and L3 nerve roots, see *Figure 5-13*, page 94 for distribution) where it enters the thigh though the opening between the inguinal ligament and its attachment to the anterior superior iliac spine **(ASIS)**. Anatomic variation is common, and the nerve may actually pass through the ligament, and as many as four branches may be found. May also be an initial manifestation of diabetes (diabetic neuropathy).

Signs and symptoms

Burning dysesthesias in the lateral aspect of the upper thigh, occasionally just above the knee, usually with increased sensitivity to clothing (hyperpathia). There may be decreased sensation in this distribution. Spontaneous rubbing or massaging the area in order to obtain relief is very characteristic[96]. MP may be bilateral in up to 20% of cases. Sitting or lying prone usually ameliorates the symptoms.

There may be point tenderness at the site of entrapment (where pressure may reproduce the pain), which is often located where the nerve exits the pelvis medial to the ASIS. Hip extension may also cause pain.

Occurrence

Usually seen in obese patients, may be exacerbated by wearing tight belts or girdles, and by prolonged standing or walking. Recently found in long distance runners. Higher incidence in diabetics. May also occur post-op in slender patients positioned prone, tends to be bilateral (*see page 800*).

Possible etiologies are too numerous to list, more common ones include: tight clothing or belts, surgical scars post-abdominal surgery, cardiac catheterization (*see page 800*), pregnancy, iliac crest bone graft harvesting, ascites, obesity, metabolic neuropathies, and abdominal or pelvic mass.

Differential diagnosis

1. femoral neuropathy: sensory changes tend to be more anteromedial than MP
2. L2 or L3 radiculopathy: look for motor weakness (thigh flexion or knee extension)
3. nerve compression by abdominal or pelvic tumor (suspected if concomitant GI or GU symptoms)

The condition can usually be diagnosed on clinical grounds. When it is felt to be necessary, confirmatory tests may help (but frequently are disappointing), including:

1. EMG: may be difficult, the electromyographer cannot always find the nerve)
2. MRI or CT/myelography: when disc disease is suspected
3. pelvic imaging (MRI or CT)
4. somatosensory evoked potentials
5. response to local anesthetic injections
6. recent promise of diagnostic ultrasound using high frequency (18 MHz) probes

Treatment

Tends to regress spontaneously, but recurrence is common. Nonsurgical measures achieve relief in ≈ 91% of cases and should be tried prior to considering surgery[97]:

1. remove offending articles (constricting belts, braces, casts, tight garments…)
2. in obese patients: weight loss and exercises to strengthen the abdominal

muscles is usually effective, but is rarely achieved by the patient

3. elimination of activities involving hip extension
4. application of ice to the area of presumed constriction **x** 30 minutes TID
5. NSAID of choice **x** 7-10 days
6. capsaicin ointment applied TID (*see page 566*)
7. lidoderm patches in areas of hyperesthesia may help[98] (*see page 549*)
8. centrally acting pain medications (e.g. gabapentin, carbamazepine…) are rarely effective
9. if the above measures fail, injection of 5-10 ml of local anesthetic (with or without steroids) at the point of tenderness, or medial to the ASIS may provide temporary or sometimes long lasting relief, and confirms the diagnosis

Surgical treatment

Options include:

1. surgical decompression (neurolysis) of the nerve: higher failure and recurrence rate than neurectomy
2. decompression and transposition
3. selective L2 nerve stimulation
4. division of the nerve (neurectomy) may be more effective, but risks denervation pain, and leaves an anesthetic area (usually a minor nuisance). May be best reserved for treatment failures

Technique[97]:

The operation is best performed under general anesthesia. A 4-6 cm oblique incision is centered 2 cm distal to the point of tenderness. Since the course of the nerve is variable, the operation is exploratory in nature, and generous exposure is required. If the nerve can't be located, it is usually because the exposure is too superficial. If the nerve still cannot be found, a small abdominal muscle incision can be made and the nerve may be located in the retroperitoneal area. CAUTION: cases have occurred where the femoral nerve has erroneously been divided.

If neurectomy instead of neurolysis is elected, electrical stimulation should be performed prior to sectioning to rule out a motor component (which would disqualify the nerve as the LFCN). If the nerve is to be divided, it should be placed on stretch and then cut to allow the proximal end to retract back into the pelvis. Any segment of apparent pathology should be resected for microscopic

analysis. Neurectomy results in anesthesia in the distribution of the LFCN that is rarely distressing and gradually reduces in size.

A supra-inguinal ligament approach has also been described[99].

OBTURATOR NERVE ENTRAPMENT

Controversial if this exists. The obturator nerve is composed of L2-4 roots. It courses along the pelvic wall to provide sensation to the inner thigh, and motor to the thigh adductors (gracilis and adductors longus, brevis, and magnus). It may be compressed by pelvic tumors, also from the pressure of the fetal head or forceps during parturition.

The result is numbness of the medial thigh and weak thigh adduction.

FEMORAL NERVE ENTRAPMENT

Composed of roots L2-4. Entrapment is a rare cause of femoral neuropathy. More commonly due to fracture or surgery. *Femoral neuropathy* on page 798.

COMMON PERONEAL NERVE PALSY

The peroneal nerve is the most common nerve to develop *acute* compression palsy.

Functional anatomy: the sciatic nerve (L4-S3) consists of 2 separate nerves within a common sheath that separate at a variable location in the thigh[A] (see *Table 35-4*, page 1195):

A. the peroneal division of the sciatic nerve is more vulnerable to injury than the tibial division

1. **posterior tibial nerve**, or, just tibial nerve (AKA medial popliteal nerve) which provides for foot inversion among other motor functions
2. **common peroneal nerve (CPN)**, or, just peroneal nerve (AKA lateral popliteal nerve): high injuries may involve the lateral hamstring (short head of the biceps femoris) in addition to the following. The CPN passes behind the fibular head where it is superficial and fixed, making it vulnerable to pressure or trauma (e.g. from crossing the legs at the knee). Just distal to this, the CPN divides into:

A. **deep peroneal nerve** (AKA anterior tibial nerve): primarily motor
   1. motor: foot and toe extension (extensor hallicus longus **(EHL)**, anterior tibialis **(AT)**, extensor digitorum longus **(EDL)**)
   2. sensory: very small area between great toe and second toe

B. **superficial peroneal nerve** (AKA musculocutaneous nerve)
   1. motor: foot eversion (peroneus longus and brevis)
   2. sensory: lateral distal leg and dorsum of foot

Table 24-20 Muscle involvement in peroneal nerve palsy

Muscle	Nerve	Action	Involvement
EHL	deep peroneal	great toe dorsiflexion	most commonly involved
anterior tibialis		ankle dorsiflexion	↓
EDL		toe extension	
peroneus longus & brevis	superficial peroneal	foot eversion	least commonly involved (often spared)

Findings in peroneal nerve palsy

- sensory changes (uncommon): involves lateral aspect of lower half of leg
- muscle involvement: *see Table 24-20*

Common peroneal nerve palsy (most common) produces weak ankle dorsiflexion (foot drop) due to anterior tibialis palsy, weak foot eversion, and sensory impairment in areas innervated by deep and superficial peroneal nerve (lateral calf and dorsum of foot). There may be a Tinel's sign with percussion over the nerve near the fibular neck. Occasionally, only the deep peroneal nerve is involved, resulting in foot drop with minimal sensory loss. Must differentiate from other causes of foot drop (see *Foot drop*, page 1194).

Examination/clinical correlation[4 (p 293)]

- **buttock** level injury: unless the injury is one that permits spontaneous regeneration, prognosis is poor for return of peroneal nerve function even with surgery
- **thigh** level injury: also difficult to get improvement with surgical repair. Some peroneus function may occur at ≥ 6 mos, early contraction of AT may take ≥ 1 yr
- **knee** level injury: with successful regeneration, peroneus contraction may

begin by 3-5 months. First signs: quivering of muscle lateral to the proximal fibula on attempted foot eversion, or tightening of tendon posterior and behind the lateral malleolus on attempted ankle dorsiflexion

Causes of common peroneal nerve injury

The most frequent cause of serious peroneal nerve injury is knee injury ± fracture (for causes of foot drop other than peroneal nerve palsy *see page 1195*).

1. entrapment as it crosses the fibular neck or as it penetrates the peroneus longus
2. diabetes mellitus and other metabolic peripheral neuropathies
3. inflammatory neuropathy: including Hansen’s disease (leprosy)
4. traumatic: e.g. clipping injury in football players, stretch injury due to dislocating force applied to the knee, fibular fracture, injury during hip or knee replacement surgery
5. penetrating injury
6. masses in the area of the fibular head/proximal lower leg: popliteal fossa cysts (Baker cyst), anterior tibial artery aneurysm[100] (rare)
7. pressure at fibular head: e.g. from crossing the legs at the knee, casts, obstetrical stirrups (*see page 799*)…
8. traction injuries: severe inversion sprains of the ankle
9. intraneural tumors: neurofibroma, schwannoma, ganglion cysts
10. vascular: venous thrombosis
11. weight loss

Evaluation

EMG: EMG takes 2-4 weeks from the onset of symptoms to become positive. Stimulate above and below fibular head for prognostic information: if absent in both sites, the prognosis is poor (indicates retrograde degeneration has occurred). Wallerian degeneration takes ≈ 5 days to cause deterioration.

In addition to the expected findings of denervation (PSWs & fibs - *see page 270*) in the anterior tibialis, evaluate:

1. L5 innervated muscles outside the distribution of the common peroneal nerve:
   A. posterior tibialis
   B. flexor digitorum longus

2. L5 muscles whose nerve originates above the knee (these muscles are spared in cases of compression of the peroneal nerve at the fibular head due to the fact that the nerve takeoff is proximal to the popliteal fossa):
   A. biceps femoris (short or long head)
   B. tensor fascia lata
3. paraspinal muscles: signs of denervation solidifies the location of the lesion as nerve root; not helpful if negative

MRI: May demonstrate causes such as a ganglion cyst arising from the superior tibiofibular articulation.

Treatment

When treatment can eliminate a reversible cause, the outcome is usually good. Surgical exploration and decompression may be considered when there is no reversible cause or when improvement does not occur.

Bracing: ankle-foot-orthosis **(AFO)** compensates for loss of ankle dorsiflexion which inserts unobtrusively into a shoe. If this is inadequate, or to stabilize the ankle, a spring-loaded kick-up foot brace built into a shoe may be used. The patient should be instructed in techniques to avoid contracture of the Achilles tendon (heel cord) which would impair ankle dorsiflexion if nerve function returns.

Surgical technique: At the level of the popliteal fossa the skin incision is made just medial to the tendon of the short head of the biceps femoris (lateral hamstring) as the peroneal nerve is best located deep to or slightly medial to this tendon. The incision is carried distally slightly laterally along the surgical neck of the fibula. The biceps femoris is retracted laterally and the nerve is isolated and tagged with a Penrose drain. The sensory sural nerve branches off the peroneal nerve at variable sites ranging from the sciatic portion of the nerve (proximal to the flexor crease) or distal to this.

In cases of compression, the fascia from the lateral gastrocnemius and soleus over-lying the nerve distal to the fibular head is lysed and the nerve is exposed in 360°. As the nerve crosses the fibular neck it divides into superficial and deep branches. The superficial branch travels directly distally to supply the peroneus longus and brevis (foot evertors). The deep branches curve anteriorly to the anterior tibialis, EHL, and toe extensors.

If a graft is needed, the contralateral sural nerve is usually used, which may be supplemented with the ipsilateral sural nerve if needed.

TARSAL TUNNEL

Entrapment of **(posterior) tibial nerve** may occur in the tarsal tunnel, posterior and inferior to medial malleolus. The tunnel is covered by the flexor retinaculum (lancinate ligament) which extends downward from the medial malleolus to the tubercle of the calcaneus. There is often (but not necessarily) a history of old ankle dislocation or fracture. The nerve may be trapped at the retinacular ligament. This results in pain and paresthesias in the toes and sole of foot (often sparing the heel because the sensory branches often originate proximal to the tunnel), typically worse at night. May cause clawing of toes secondary to weakness of intrinsic foot muscles. Often caused by fracture or dislocation, also rheumatoid arthritis, rarely tumors.

Exam

Percussion of nerve at medial malleolus produces paresthesias that radiate distally (Tinel's sign). Maximal inversion and eversion of the foot tend to exacerbate. **Dorsiflexion-eversion test**: examiner maximally everts and dorsiflexes the ankle while dorsiflexing the toes at the MTP joints for 5-10 seconds. Positive test reproduces the pain.

Diagnosis

EMG and NCV studies may help.

Treatment

External ankle support to improve foot mechanics.

Surgical decompression is indicated for confirmed cases that fail to improve. A curvilinear incision is used, ≈ 1.5 cm posterior and inferior to the medial malleolus. The flex-or retinaculum is divided, as are any septa underneath, and the distal branches should be followed until they dive into the muscle.

24.4. Thoracic outlet syndrome

The thoracic outlet is a confined area at the apex of the lung bordered by the 1st rib below and the clavicle above through which passes the subclavian artery, vein, and brachial plexus.

Thoracic outlet syndrome **(TOS)** is a term implying compression of one or more of the enclosed structures producing a heterogeneous group of disorders. TOS tends to be diagnosed more often by general and vascular surgeons than by neurologists and neurosurgeons. Four unrelated conditions with different structures involved:

1. arterial vascular: producing arm, hand and finger pallor and ischemia } "noncontroversial", with characteristic symptom complex, reproducible clinical findings, confirmatory laboratory tests. Low incidence[101]
2. venous vascular: producing arm swelling and edema } "noncontroversial", with characteristic symptom complex, reproducible clinical findings, confirmatory laboratory tests. Low incidence[101]
3. true neurologic: compressing the lower trunk or median cord of the brachial plexus (*see below*) } "noncontroversial", with characteristic symptom complex, reproducible clinical findings, confirmatory laboratory tests. Low incidence[101]
4. disputed neurologic: (*see below*) } "noncontroversial", with characteristic symptom complex, reproducible clinical findings, confirmatory laboratory tests. Low incidence[101]

Differential diagnosis

1. herniated cervical disc
2. cervical arthrosis
3. lung cancer (pancoast tumor)
4. tardy ulnar nerve palsy
5. carpal tunnel syndrome
6. orthopedic shoulder problems
7. complex regional pain syndrome (reflex sympathetic dystrophy)

TRUE NEUROLOGIC TOS

A rare condition primarily affecting adult women, usually unilateral.

Neurologic structures involved

1. most common: compression of the C8/T1 roots
2. or proximal lower trunk of the brachial plexus **(BP)**
3. less common: compression of the median cord of the BP

Etiologies

1. constricting band extending from the first rib to a rudimentary "cervical rib" or to an elongated C7 transverse process
2. scalenus (anticus) syndrome: controversial (see *Scalenus (anticus) syndrome (disputed neurologic TOS)* below)
3. compression beneath the pectoralis minor tendon under the coracoid process: may result from repetitive movements of the arms above the head (shoulder elevation and hyperabduction)

Signs & symptoms include:
1. ★ sensory changes in distribution of median cord (mainly along medial forearm), <u>sparing</u> median nerve sensory fibers (pass through upper and middle trunks)
2. hand clumsiness or weakness and wasting, especially abductor pollicis brevis and ulnar hand intrinsics (C8/T1 denervation/atrophy)
3. there may be tenderness over Erb's point (2 to 3 cm above the clavicle in front of the C6 transverse process)
4. may be painless
5. usually unilateral

Confirmatory tests:
1. EMG: unreliable (may be negative). Most common abnormality in neurogenic TOS is loss of medial antebrachial cutaneous SNAP
2. MRI does not show bony abnormalities well, but may occasionally demonstrate a kink in the lower BP. Can also rule-out conditions that may mimic TOS such as herniated cervical disc
3. cervical spine x-rays with obliques and apical lordotic CXR may demonstrate bony abnormalities. However, not every cervical rib produces symptoms.

Treatment

Controversial. Conservative treatment (usually including stretching and physical therapy) is about as effective as surgery and avoids attendant risks.

Decompression can be achieved by removing the muscles that surround the nerves (scalenectomy), by transaxillary first rib resection, or both.

SCALENUS (ANTICUS) SYNDROME (DISPUTED NEUROLOGIC TOS)

Controversial. More commonly diagnosed in the 1940's and 50's. There is a lack of consensus regarding the pathophysiology (including structures involved),

clinical presentation, helpful tests, and optimal treatment. Removal of first thoracic rib is often advocated for treatment, frequently via a transaxillary approach. Unfortunately, injuries, especially to the lower trunk of the brachial plexus, may result from the surgery.

Other variations include an “upper plexus” type for which total anterior scalenectomy is advocated. Again, very controversial.

24.5. Miscellaneous peripheral nerve

Nerve block

For example, to block greater occipital nerve in occipital neuralgia.

Rx: add 40 mg methylprednisolone aqueous suspension (Depo-Medrol®) to 10 ml of 0.75% bipuvicaine (Marcaine®) and inject into region of irritated or inflamed nerve.

24.6. References

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NOTES

25. Neurophthalmology

25.1. Nystagmus

Involuntary rhythmic oscillation of the eyes, usually conjugate. Most common form is jerk nystagmus, in which the direction of the nystagmus is defined for the direction of the fast (cortical) component (which is not the abnormal component). Horizontal or upward gaze-provoked nystagmus may be due to sedatives or AEDs; otherwise **vertical nystagmus** is indicative of posterior fossa pathology.

LOCALIZING LESION FOR VARIOUS FORMS OF NYSTAGMUS

1. **seesaw nystagmus**: intorting eye moves up, extorting eye moves down, pattern then reverses. Lesion in diencephalon. Also reported with chiasmal compression (occasionally accompanied with bitemporal hemianopia in parasellar masses)
2. **convergence nystagmus**: slow abduction of eyes followed by adducting (converging) jerks, usually associated with features of Parinaud's syndrome. May be associated with nystagmus retractorius (*see below*) with similar location of lesion
3. **nystagmus retractorius**: resulting from co-contraction of all EOM's. May accompany convergence nystagmus. Lesion in upper midbrain tegmentum (usually vascular disease or tumor, especially pinealoma)
4. **downbeat nystagmus**: nystagmus with the fast phase downward while in primary position. Most patients have a structural lesion in the posterior fossa, especially at the cervicomedullary junction (foramen magnum **(FM)**)[1], including Chiari I malformation, basilar impression, p-fossa tumors, syringobulbia[2]. Uncommonly occurs in multiple sclerosis, spinocerebellar degeneration, and in some metabolic conditions (hypomagnesemia, thiamine deficiency, alcohol intoxication or withdrawal, or treatment with phenytoin, carbamazepine or lithium[3])
5. **upbeat nystagmus**: lesion in medulla
6. **abducting** nystagmus occurs in INO. Lesion in pons (MLF)

7. **Brun's** nystagmus: lesion in pontomedullary junction **(PMJ)**
8. **vestibular** nystagmus: lesion in PMJ
9. **ocular myoclonus**: lesion in myoclonic triangle
10. **periodic alternating** nystagmus **(PAN)**: lesion in FM and cerebellum
11. **square wave jerks**, macro square wave jerks, macro saccadic oscillations. Lesion in cerebellar pathways
12. "nystagmoid" eye movements (not true nystagmus)
    A. **ocular bobbing**: lesion in pontine tegmentum (*see page 838*)
    B. **ocular dysmetria**: overshoot of eye on attempted fixation followed by diminishing oscillations until eye "hones in" on target. Lesion in cerebellum or pathways (may be seen in Friedreich's ataxia)
    C. ping-pong gaze: *see page 283*
    D. "windshield wiper eyes": *see page 283*

25.2. Papilledema

AKA choked (optic) disk. Thought to be caused by axoplasmic stasis. One theory: elevated ICP is transmitted through the subarachnoid space of the optic nerve sheath to the region of the optic disc. Elevated ICP will usually obliterate retinal venous pulsation if the pressure is transmitted to the point where the central retinal vein passes through the subarachnoid space ($\approx$ 1 cm posterior to the globe). Papilledema may also be dependent on the ratio of retinal arterial to retinal venous pressure, with ratios < 1.5:1 more commonly associated with papilledema than higher ratios.

Elevated ICP generally causes bilateral papilledema (*see below* for *unilateral* papilledema). Papilledema may appear similar to optic neuritis on funduscopy, but the latter is usually associated with more severe visual loss and tenderness to pressure over the eye.

Papilledema typically takes 24-48 hours to develop following a sustained rise in ICP. It is rarely seen as early as $\approx$ 6 hours after onset, but not earlier. Papilledema does not cause visual blurring or reduction of visual fields unless very severe and prolonged.

Differential diagnosis of unilateral papilledema:

1. compressive lesions
    A. orbital tumors

B. tumors of optic nerve sheath (meningiomas)

C. optic nerve tumors (optic gliomas)

2. local inflammatory disorder
3. Foster Kennedy syndrome: *see page 112*
4. demyelinating disease (e.g. multiple sclerosis)
5. elevated ICP (as in pseudotumor cerebri) with some form of blockage on the normal appearing side which prevents transmission of elevated CSF pressure to that optic disc[4]
6. eye prosthesis (artificial eye)

25.3. Visual fields

Normal human visual field: extends approximately from 35° nasally in each eye, to 90°temporally, and 50° above and below the horizontal meridian. The normal physiological blind spot (due to absence of light receptors in the optic disc due to penetration of the retina by the optic nerve and vessels) is located to the temporal side of the macular visual area in each eye.

Macular sparing/splitting

Macular splitting can occur both in lesions both anterior or posterior to the lateral geniculate body (LGB). However, macular sparing tends to occur with lesions posterior to the LGB. Homonymous hemiaopsia with macular sparing tends to occur with lesions in the optic radiation or infarcts of primary visual cortex. There is more than 1 way for this to occur: input from the macula is spread over a large portion of the optic radiation and primary visual cortex, and the occipital pole (primary visual cortex) receives dual blood supply.

25.3.1. Visual field deficits

Can be tested by:

1. bedside confrontational testing: detects only gross peripheral field deficits.
2. formal perimetry

   A. using a tangent screen

   B. Goldmann perimetry

C. automated perimetry exam: Humphrey visual field **(HVF)**

Knee of Wilbrand (named for Hermann Wilbrand (1851-1935) German neurophthalmologist). Some controversy as to existence.

Visual field deficit patterns

1. bitemporal hemianopsia
2. posterior cerebral artery occlusion → infarction in the anterior visual cortex → contralateral homonymous hemianopia with macular *sparing*

25.4. Pupillary diameter

PUPILODILATOR (SYMPATHETIC)

Pupilodilator muscle fibers are sympathetic and are arranged radially in the iris.

First-order sympathetic nerve fibers arise in the posterolateral hypothalamus, and descend uncrossed in the lateral tegmentum of the midbrain, pons, medulla and cervical spinal cord to the intermediolateral cell column of the spinal cord from C8-T2 (ciliospinal center of Budge). Here they synapse with lateral horn cells (neurotransmitter: ACh) and give off 2nd order neurons (preganglionics).

Second-order neurons enter the sympathetic chain and ascend but do not synapse until they reach the superior cervical ganglion, where they give rise to 3rd order neurons.

Third-order neurons (postganglionics) course upward with the common carotid artery, those that mediate sweat in the face split off with the ECA. The rest travel with the ICA passing over the carotid sinus. Some fibers accompany V1 (ophthalmic division of trigeminal nerve), passing through (without synapsing) the ciliary ganglion, reaching the pupilodilator muscle of the eye as 2 long ciliary nerves (neurotransmitter: NE). Other fibers from the ICA travel with the ophthalmic artery to innervate the lacrimal gland and Müller's muscle (AKA the orbital muscle).

PUPILLOCONSTRICTOR (PARASYMPATHETIC)

Pupilloconstrictor muscle fibers are arranged as a sphincter in the iris.

Parasympathetic preganglionic fibers arise in the Edinger-Westphal nucleus (in high midbrain, superior colliculus level) and are situated peripherally on the

intracranial portion of the oculomotor nerve (*see page 834*).

Pupillary light reflex

Mediated by rods and cones of the retina which are stimulated by light, and transmit via their axons in the optic nerve. As with the visual path, temporal retinal fibers remain ipsilateral, whereas nasal retinal fibers decussate in the optic chiasm. Fibers subserving the light reflex bypass the lateral geniculate body **(LGB)** (unlike fibers for vision which enter the LGB) to synapse in the **pretectal nuclear complex** at the level of the superior colliculus. Intercalating neurons connect to both Edinger-Westphal para-sympathetic motor nuclei. The preganglionic fibers travel within the third nerve to the ciliary ganglion as described above under *Pupilloconstrictor (parasympathetic)*.

Monocular light normally stimulates bilaterally symmetric (i.e. equal) pupillary constriction (ipsilateral response is called *direct*, contralateral response is *consensual*).

Pupillary exam

To perform a complete bedside pupillary exam[A]:

A. see following sections for rationale for various aspects of the pupillary exam

1. measure pupil size in a darkened room: anisocoria augmented in the dark indicates the smaller pupil is abnormal and suggests a sympathetic lesion
2. measure pupil size in a lighted room: anisocoria intensified in the light suggests the larger pupil is abnormal and that the defect is in the parasympathetics
3. note the reaction to bright light (direct and consensual)
4. near response (it is necessary to check this only if the light reaction is not good): the pupil normally constricts on convergence, and this response should be greater than the light reflex (accommodation is not necessary, and a visually handicapped patient can be instructed to follow their own finger as it is brought in)
   A. **light-near dissociation**: pupillary constriction on convergence but absent light response (**Argyll Robertson pupil**). Etiologies:
      1. classically described in syphilis
      2. Parinaud's syndrome: dorsal midbrain lesion (*see page 114*)

    3. oculomotor neuropathy (usually causes a tonic pupil as in oculomotor compression, *see below*): DM, EtOH
    4. Adie's pupil: *see below*
5. **swinging flashlight test**: alternate the flashlight from one eye to the other with as little delay as possible; watch ≥ 5 seconds for the pupil to redilate (dilation after initial constriction is called **pupillary escape** and is normal - due to retinal adaptation). Normal: direct and consensual light reflexes are equal. **Afferent pupillary defect** (*see below*): consensual reflex is stronger than the direct (i.e. pupil is larger on direct illumination than contralateral illumination)

25.4.1. Alterations in pupillary diameter

ANISOCORIA

Definition: unequal pupil sizes (usually ≥ 1 mm difference).

An afferent pupillary defect **(APD)** (even with total blindness in one eye) alone does <u>not</u> produce anisocoria (i.e. an APD together with anisocoria indicates two separate lesions (*see below*)).

Evaluation

1. history is critically important. Check for exposure to drugs that affect pupillary size, trauma. Look at old photos (e.g. driver's license) for physiologic anisocoria
2. exam: see *Pupillary exam* above
3. a non-contrast CT is usually not helpful and can provide a false sense of security

Differential diagnosis:

1. physiologic anisocoria: occurs in ≈ 20% of population (more common in people with a light iris). Familial and nonfamilial varieties exist. The difference in pupils is usually < 0.4 mm. The inequality is the same in a light and dark room (or slightly worse in the dark)
2. pharmacologic pupil (*see below*): the most common cause of <u>sudden onset</u> of anisocoria

A. mydriatics (pupillary dilators):
   1. sympathomimetics (stimulate the dilator pupillae): usually cause only 1-2 mm of dilation, may react slightly to light. Includes: phenylephrine, clonidine, naphazoline (an ingredient in OTC eye drops for allergies), eye contact with cocaine, certain plants (e.g. jimsonweed)
   2. parasympatholytics (inhibit the sphincter pupillae): cause maximal dilation (up to 8 mm) that does not react to light. Includes: tropicamide, atropine, scopolamine (including patches for motion sickness), certain plants (e.g. deadly nightshade)

B. miotics (pupillary constrictors): pilocarpine, organophosphates (pesticides), flea powders containing anticholinesterase

3. Horner's syndrome: interruption of sympathetics to pupilodilator. The abnormal pupil is the smaller (miotic) pupil. If there is ptosis it will be on the side of the small pupil. For etiologies, etc., *see page 833*
4. third nerve palsy (*see page 834*). If there is ptosis, it will be on the side of the large pupil
   A. oculomotor neuropathy ("peripheral" neuropathy of the third nerve): usually spares the pupil. Etiologies: DM (usually resolves in ≈ 8 weeks), EtOH…
   B. third nerve compression: tends not to spare pupil (i.e. pupil is dilated). Produces loss of parasympathetic tone. Etiologies include:
      1. aneurysm:
         a. p-comm: the most common aneurysm to cause this
         b. basilar bifurcation: occasionally compresses posterior III nerve
      2. uncal herniation: see *Oculomotor nerve compression* below
      3. tumor
      4. cavernous sinus lesions: including cavernous internal carotid aneurysm, carotid-cavernous fistula, cavernous sinus tumors
5. Adie's pupil (AKA tonic pupil): *see below*
6. local trauma to the eye: traumatic iridoplegia. Injury to the pupillary sphincter muscle may produce mydriasis or less often miosis, shape may be irregular
7. pontine lesions
8. eye prosthesis (artificial eye) AKA pseudoanisocoria
9. occasionally some patients have anisocoria that occurs only during migraine[5]
10. iritis

11. keratitis or corneal abrasion

Marcus Gunn pupil

AKA (relative) **afferent pupillary defect (APD** or **RAPD)**, AKA amaurotic pupil. Finding: consensual pupillary reflex to light is stronger than the direct (normal responses are equal). Contrary to some textbooks, the amaurotic pupil is not larger than the other[6]. The presence of the consensual reflex is evidence of a preserved third nerve (with parasympathetics) on the side of the impaired direct reflex. Best detected with the swinging flashlight test (*see above*).

Etiologies

Lesion anterior to the chiasm ipsilateral to the side of the impaired direct reflex:

1. either in the retina (e.g. retinal detachment, retinal infarct e.g. from embolus)
2. or optic nerve, as may occur in:
   A. optic or retrobulbar neuritis: commonly seen in MS, but may also occur after vaccinations or viral infections, and usually improves gradually
   B. trauma to the optic nerve: indirect (*see page 863*) or direct
   C. compression by tumor anterior to the chiasm

Adie's pupil (tonic pupil)

An iris palsy resulting in a dilated pupil, due to impaired postganglionic parasympathetics. Thought to be due to a viral infection of the ciliary ganglion. When associated with loss of all muscle tendon reflexes it is called Holmes-Adie's (is not limited to knee jerks, as some texts indicate). Typically seen in a woman in her twenties.

Slit-lamp exam shows some parts of iris contract and others don't.

These patients exhibit light-near dissociation (*see above*): in checking near response it is necessary to wait a few seconds.

Denervation supersensitivity: usually occurs after several weeks (not in acute phase). Administer two drops of dilute pilocarpine (0.1-0.125%), a parasympathomimetic in each eye. Miosis (constriction) will occur in Adie's pupil within 30 minutes (normal pupils will react only to ≈ 1% pilocarpine).

Pharmacologic pupil

Follows administration of a mydriatic agent. The mydriatic agent may be

"occult" when other care providers have not been alerted that this has been used, or when health care personnel unwittingly inoculate agents, e.g. scopolamine, atropine[7]… into a patient's eye or into their own eye. May present with accompanying H/A, and if it is unknown that a mydriatic is involved, this may be misinterpreted e.g. as a warning of an expanding p-comm aneurysm.

A pharmacologically dilated pupil is very large (7-8 mm), and is larger than typical mydriasis due to third nerve compression (5-6 mm).

To differentiate pharmacologic pupil from a third nerve lesion: instill 1% pilocarpine (a parasympathomimetic) in both eyes (for comparison). A pharmacologic pupil does not constrict, whereas the normal side and a dilated pupil from a third nerve palsy will.

Agents: Drugs intentionally used by physicians to dilate the pupils (e.g. Mydriacyl, *see below*). For other mydriatics, *see above*.

Management: Option: admit and observe overnight, pupil should normalize.

Using mydriatic agents to produce pupillary dilatation

Indications: to improve the ability to examine the retina. NB: ability to follow bedside examination of pupils will be lost for duration of drug effect. This could mask pupillary dilatation from third nerve compression due to herniation (*see page 286* and *page 287*). Always alert other caregivers and place a note in the chart that the pupil has been pharmacologically dilated (*see above*), including the agent(s) used and the time administered.

Rx: 2 gtt of 0.5% or 1% tropicamide (Mydriacyl®) blocks the parasympathetic supply to pupil, and produces a mydriasis that lasts a couple hrs to half a day. This can be augmented with 1 gtt 2.5% phenylephrine ophthalmic (Mydfrin®, Neofrin®, Phenoptic® and others) which stimulates the sympathetics.

Oculomotor nerve compression

Third nerve compression may manifest initially with a mildly dilated pupil (5-6 mm). Possible etiologies include uncal herniation or expansion of a p-comm or basilar bifurcation aneurysm. However, within 24 hours, most of these cases will also develop an oculomotor palsy (with down and out deviation of the eye and ptosis). These pupils respond to mydriatics and to miotic agents (the latter helps differentiate this from a pharmacologic pupil, *see above*).

Although it is possible for a unilaterally dilated pupil alone to be the initial presentation in uncal herniation, in actuality almost all of these patients will have

some other finding, e.g. alteration in mental status (confusion, agitation, etc.) before midbrain compression occurs (i.e. it would be rare for a person undergoing early uncal herniation with a dilating pupil to be awake, talking, appropriate and neurologically intact).

NEUROMUSCULAR BLOCKING AGENTS (NMBAS)

Due to the absence of nicotinic receptors on the iris, non-depolarizing muscle blocking agents, such as pancuronium (Pavulon®) do not alter pupillary reaction to light[8] except in large doses where some of the first and second order neurons may be blocked.

PARADOXICAL PUPILLARY REACTION

Pupils constrict when light is removed.

1. congenital stationary night blindness
2. Best disease: autosomal dominant hereditary progressive macular dystrophy
3. optic nerve hypoplasia
4. retinitis pigmentosa

HORNER'S SYNDROME

Horner's syndrome **(HS)** is caused by interruption of sympathetics to the eye and face anywhere along their path (see *Pupilodilator (sympathetic)*, page 829). Unilateral findings on the involved side in a fully developed Horner's syndrome are shown in *Table 25-1*.

Table 25-1 Findings in Horner's syndrome

- miosis (constricted pupil)
- ptosis
- enophthalmos
- hyperemia of eye
- anhidrosis of half of face

Miosis (pupillary constriction) in HS

The miosis in Horner's syndrome is only ≈ 2-3 mm. This will be accentuated by darkening the room, which causes the normal pupil to dilate.

Ptosis and enophthalmos

Ptosis is due primarily to paralysis of the superior and inferior tarsal muscles (weakness of the inferior tarsal muscle is technically called “inverse ptosis”). Enophthalmos is due to **Müller’s muscle** paralysis, which also contributes a maximum of ≈ 2 mm to the ptosis. Ptosis in HS is partial, c.f. complete ptosis which is due to weakness of levator palpebra superioris which is not involved in Horner’s syndrome.

POSSIBLE SITES OF DISRUPTION OF SYMPATHETICS

See *page 829* for anatomy of 1st, 2nd, and 3rd order sympathetic neurons.

1st order neuron (central neuron): Interruption is often accompanied by other brainstem abnormalities. Etiologies of dysfunction: infarction from vascular occlusion (usually PICA), syringobulbia, intraparenchymal neoplasm.

2nd order neuron (preganglionic): Etiologies of dysfunction: lateral sympathectomies, significant chest trauma, apical pulmonary neoplasms[9] (Pancoast tumor), high thoracic or cervical neuroblastoma.

3rd order neuron (postganglionic): The most common type. Etiologies of dysfunction: neck trauma, carotid vascular disease/studies (e.g. carotid dissections, *see page 1162*), cervical bony abnormalities, migraine, skull base neoplasms, cavernous sinus lesions (e.g. meningioma). With involvement only of fibers on ICA, anhidrosis does not occur (i.e. sweating is preserved) on ipsilateral face since fibers to facial sweat glands travel with ECA.

PHARMACOLOGIC TESTING IN HORNER’S SYNDROME

Establishing the diagnosis

If the diagnosis of Horner’s syndrome is in doubt, the following may be used (not necessary when a pupil lag upon darkening the room can be demonstrated in the affected eye) (does not localize lesion as 1st order, etc.).

Cocaine. ***Rx***: 1 gtt 4% cocaine OU (not the 10% solution that is commonly used in ENT procedures which will also anesthetize the sphincter pupillae, thus preventing miosis), repeat in 10 min. Observe pupils over 30 min. Cocaine blocks the NE re-uptake of postganglionics at the neuroeffector junction. In HS, no NE is released and cocaine will not dilate eye. If pupil dilates normally, no HS. Delayed dilatation occurs in partial HS.

Apraclonidine ophthalmic (Iopidine®) has essentially replaced cocaine for

establishing diagnosis. Iopidine causes the miotic pupil to dilate in Horner's syndrome due to denervation hypersensitivity in the pupilodilator muscle fibers.

Localizing the site of the lesion

First order HS usually is accompanied by other hypothalamic, brainstem, or medullary findings.

To differentiate a second from third-order: 1% hydroxyamphetamine (Paradrine®) releases NE from nerve endings at neuroeffector junction causing dilation of pupil except in 3rd order neuron lesions (injured postganglionics do not release NE).

25.5. Extraocular muscle (EOM) system

Cr. N. III (oculomotor) innervates the ipsilateral medial rectus **(MR)**, inferior rectus **(IR)**, inferior oblique **(IO)**, and superior rectus **(SR)**. Cr. N IV (trochlear) innervates the ipsilateral superior oblique **(SO)**, contralateral to the trochlear nucleus (*see page 835*). Cr. N. VI (abducens) innervates the ipsilateral lateral rectus **(LR)**.

The **frontal eye field** is the cortical area that initiates voluntary (supranuclear) lateral saccadic eye movements ("pre-programmed", rapid, ballistic) to the opposite side, involved in suppressing reflexive saccades and generating voluntary, non-visual saccades. It is located in Brodmann's area 8 (in the frontal lobe, anterior to the primary motor cortex, see *Figure 5-1*, page 84). These corticobulbar fibers pass through the genu of the internal capsule to the paramedian pontine reticular formation **(PPRF)**, which controls horizontal gaze, which sends fibers to the ipsilateral abducens/para-abducens (VI) nuclear complex, and via the medial longitudinal fasciculus **(MLF)** to the contralateral III nucleus to innervate the contralateral MR. Inhibitory fibers go to the ipsilateral third nerve to inhibit the antagonist MR muscle. Thus, the right PPRF controls lateral eye movements to right.

INTERNUCLEAR OPHTHALMOPLEGIA

Internuclear ophthalmoplegia **(INO)** is due to a lesion of the MLF (*see above*) rostral to the abducens nucleus. Findings (*see Figure 25-1* for illustration):

1. on attempting to look to the side contralateral to the INO:

A. the eye ipsilateral to the lesion fails to ADDuct completely

B. abduction nystagmus in the contralateral eye (monocular nystagmus) often with some weakness of ABDuction

2. convergence is not impaired in isolated MLF lesions (INO is not an EOM palsy)

The most common causes of INO:

1. MS: the most common cause of bilateral INO in young adults
2. brainstem stroke: the most common cause of unilateral INO in the elderly

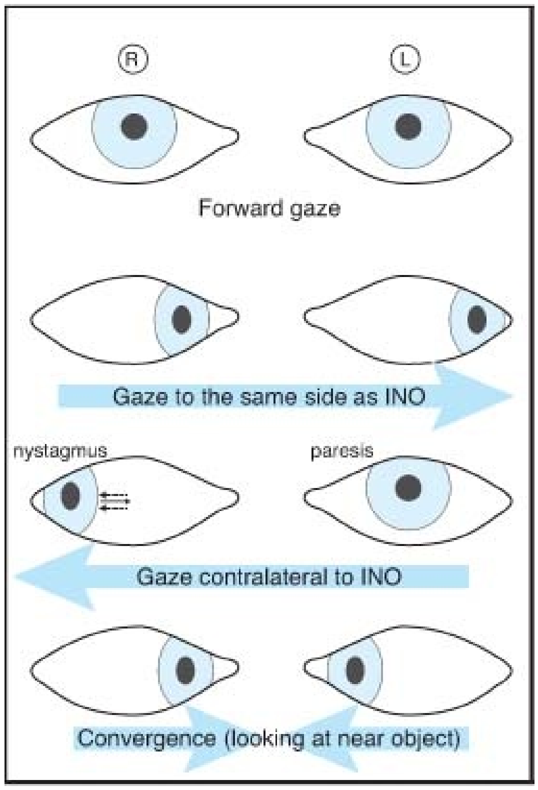

Figure 25-1 Illustration of gaze findings with a left internuclear ophthalmoplegia

OCULOMOTOR (CR. N. III) NERVE PALSY (OMP)

The oculomotor nerve exits the brain-stem ventrally and has two components: motor neurons which originate in the oculomotor nucleus, and more peripherally situated parasympathetic fibers which arise from the **Edinger-Westphal nucleus**. The nerve passes through the cavernous sinus and enters the superior orbital fissure where it divides into a superior division (innervating the superior rectus and the levator palpebrae superioris) and an inferior division (supplying the medial rectus, inferior rectus and inferior oblique). The

parasympathetic fibers travel with the inferior division and branch off to the ciliary ganglion where they synapse. Postganglionic fibers enter the posterior globe to innervate the ciliary muscle (relaxes the lens which “thickens” and accommodates for near vision) and the constrictor pupillae muscle.

Oculomotor nerve motor palsy causes ptosis with eye deviated “down & out”. Nuclear involvement of 3rd nerve is rare. NB: 3rd nerve palsy alone can cause up to 3 mm exophthalmos (proptosis) from relaxation of the rectus muscles.

Also see *Painful ophthalmoplegia* and *Painless ophthalmoplegia* below. For brainstem syndromes, see *Benedikt’s syndrome*, page 114 and *Weber’s syndrome* on page 114. Also, see *Anisocoria*, page 831.

Non pupil-sparing oculomotor palsy

The rule of the pupil in third nerve palsy: Elucidated in 1958 by Rucker. In effect, states “Third nerve palsy due to extrinsic compression of the nerve will be associated with impaired pupillary constriction.” However, in 3% the pupil is spared[10].

Etiologies (most cases are due to extrinsic compression of 3rd nerve):

1. tumor: the most common tumors affecting 3rd nerve:
   A. chordomas
   B. clival meningiomas
2. vascular: the most common vascular lesions:
   A. aneurysms of p-comm artery (pupil sparing with aneurysmal oculomotor palsy occurs in < 1%). ★ Development of a new 3rd nerve palsy ipsilateral to a p-comm aneurysm may be a sign of expansion with the possibility of imminent rupture, and is traditionally considered an indication for urgent treatment (*see page 1061*)
   B. aneurysms of the distal basilar artery or bifurcation (basilar tip)
   C. carotid-cavernous fistula: look for pulsatile proptosis (*see page 1113*)
3. uncal herniation
4. cavernous sinus lesions: usually cause additional cranial nerve findings (V_1, V_2, IV, VI; see *Cavernous sinus syndrome*, page 1204). Classically the third nerve palsy e.g. from enlarging cavernous aneurysm will not produce a dilated pupil because the sympathetics which dilate the pupil are also paralyzed[1 (p 1492)]

Pupil sparing oculomotor palsy (pupil reacts to light)

Usually from intrinsic vascular lesions occluding vaso-nervorum causing central ischemic infarction. Spares parasympathetic fibers located peripherally in 3rd nerve in 62-83% of cases[10]. Etiologies include:

1. diabetic neuropathy
2. atherosclerosis (as seen in chronic HTN)
3. vasculopathies: including giant cell arteritis (temporal arteritis) - *see page 74*
4. chronic progressive ophthalmoplegia: usually bilateral
5. myasthenia gravis

Rarely, pupil-sparing OMP has been described following an intra-axial lesion, as in a midbrain infarction[11].

Other causes of oculomotor palsy

Trauma, uncal herniation, laterally expanding pituitary adenomas, Lyme disease, cavernous sinus lesions: usually cause additional cranial nerve findings (see *Multiple cranial nerve palsies (cranial neuropathies)*, page 1202).

Lesions within the orbit tend to affect 3rd nerve branches unequally. Superior division lesion → ptosis and impaired elevation; inferior division lesion → impairment of depression, adduction and pupillary reaction.

TROCHLEAR NERVE (IV) PALSY

Anatomy: the trochlear nucleus lies ventral to the cerebral aqueduct at the level of the inferior colliculi. Trochlear nerve axons pass dorsally around the aqueduct and decussate internally just caudal to the inferior colliculi. The nerve innervates the superior oblique muscle which primarily depresses the adducted eye, but in primary gaze it intorts and secondarily abducts and depresses the globe (i.e. it moves the eye down & out).

Some unique features of the trochlear nerve:

1. the only cranial nerve to decussate internally (i.e. the trochlear nucleus is on the contralateral side to the nerve that exits and to the superior oblique it goes to)
2. the only cranial nerve to exit posteriorly on the brain stem
3. the only cranial nerve passing through the superior orbital fissure that does not pass through the annulus of Zinn (AKA annulus tendineus or annular

tendon)

Palsy results in eye deviation “up and in”. Patients tend to spontaneously tilt the head to the side opposite the IV palsy to “intort” the paretic eye and eliminate the diplopia. Diplopia is exacerbated when looking down (e.g. on descending stairs) especially when also looking inward, or when the examiner tilts the head towards the paretic side.

Isolated fourth nerve palsy is uncommon. It may occasionally occur with lesions of the cerebral peduncle or injury to the floor of the fourth ventricle near the aqueduct.

ABDUCENS (VI) PALSY

Produces a lateral rectus palsy. Clinically produces diplopia that is exaggerated with lateral gaze to the side of the palsy. Etiologies of isolated 6th nerve palsy include[12]:

1. vasculopathy: including diabetes and giant cell arteritis. Most cases resolve within 3 months (alternative cause should be sought in cases lasting longer)
2. **increased intracranial pressure**: palsy may occur with increased ICP even in the absence of direct compression of the nerve (a “false localizing” sign in this setting). Postulated to occur due to the fact that the VI nerve has a long intracranial course which may render it more sensitive to increased pressure. May be bilateral. Etiologies include:
   A. traumatically increased ICP: *see page 856*
   B. increased ICP due to hydrocephalus (e.g. from p-fossa tumor): *see page 586*
   C. idiopathic intracranial hypertension (pseudotumor cerebri): *see page 713*
3. cavernous sinus lesions: cavernous carotid aneurysm (*see page 1079*), neoplasm (meningioma…), carotid cavernous fistula (*see page 1113*)
4. inflammatory:
   A. Gradenigo’s syndrome (involvement at Dorello’s canal): *see page 838*
   B. sphenoid sinusitis: (involvement at Dorello’s canal)
5. intracranial neoplasm: e.g. clivus chordoma, chondrosarcoma
6. pseudoabducens palsy: may be due to
   A. thyroid eye disease: the most common cause of chronic VI palsy. Will have positive forced duction test (eye cannot be moved by examiner)
   B. myasthenia gravis: responds to edrophonium (Tensilon®) test

C. long-standing strabismus
D. Duane's syndrome
E. fracture of the medial wall of the orbit with medial rectus entrapment

7. following lumbar puncture: almost invariably unilateral (*see page 203*)
8. fracture through clivus: *see page 888*
9. idiopathic

MULTIPLE EXTRAOCULAR MOTOR NERVE INVOLVEMENT

Lesions in cavernous sinus (*see below*) involve cranial nerves III, IV, VI and V_1 & V_2 (ophthalmic and maxillary divisions of trigeminal nerve), and spare II and V_3.

Superior orbital fissure syndrome: dysfunction of nerves III, IV, VI and V_1.

Orbital apex syndrome: involves II, III, IV, VI and partial V_1.

4th nerve palsy may result from a contrecoup injury in frontal head trauma.

PAINFUL OPHTHALMOPLEGIA

Definition: pain and dysfunction of ocular motility (may be due to involvement of one or more of cranial nerves III, IV, V & VI).

ETIOLOGIES

1. intraorbital
   A. inflammatory pseudotumor (idiopathic orbital inflammation): *see below*
   B. contiguous sinusitis
   C. invasive fungal sinus infection producing orbital apex syndrome. Rhinocerebral mucormycosis (AKA zygomycosis): sinusitis with painless black palatal or nasal septal ulcer or eschar with hyphal invasion of blood vessels by fungi of the order *Mucorales*, especially *rhizopus*[13]. Usually seen in diabetic or immunocompromised patients, occasionally in otherwise healthy patients[14]. Often involves dural sinuses and may cause cavernous sinus thrombosis
   D. mets
   E. lymphoma
2. superior orbital fissure/anterior cavernous sinus
   A. Tolosa-Hunt syndrome: *see below*

B. mets
C. nasopharyngeal Ca
D. lymphoma
E. herpes zoster
F. carotid-cavernous fistula
G. cavernous sinus thrombosis
H. intracavernous aneurysm

3. parasellar region
    A. pituitary adenoma
    B. mets
    C. nasopharyngeal Ca
    D. sphenoid sinus mucocele
    E. meningioma/chordoma
    F. apical petrositis (Gradenigo's syndrome): *see below*
4. posterior fossa
    A. p-comm aneurysm
    B. basilar artery aneurysm (rare)
5. miscellaneous
    A. diabetic ophthalmoplegia
    B. migrainous ophthalmoplegia
    C. cranial arteritis
    D. tuberculous meningitis: may cause ophthalmoplegia, usually incomplete, most often primarily oculomotor nerve

PAINLESS OPHTHALMOPLEGIA

Differential diagnosis:

1. chronic progressive ophthalmoplegia: pupil sparing, usually bilateral, slowly progressive
2. myasthenia gravis: pupil sparing, responds to edrophonium (Tensilon®) test
3. myositis: usually also produces symptoms in other organ systems (heart, gonads…)

PSEUDOTUMOR (OF THE ORBIT)

AKA "**chronic granuloma**" (a misnomer, since true epithelioid granulomas are rarely found). An idiopathic inflammatory disease confined to the orbit that

may mimic a true neoplasm. Lymphocytic infiltration of extraocular muscles. Usually unilateral.

Typically presents with rapid onset of proptosis, pain, and EOM dysfunction (painful ophthalmoplegia with diplopia). Often follows URI, may be associated with scleral inflammation. Most commonly involves the superior orbital tissues.

Differential diagnosis:

See *Orbital lesions* on page 1218 for list.

Key points for Graves' disease **(GD)**: the histologic appearance of GD (hyperthyroidism) may be indistinguishable from pseudotumor. Involvement with GD is usually bilateral.

Treatment

Surgery tends to cause a flare up, and is thus usually best avoided.

Steroids are the treatment of choice. ***Rx***: 50-80 mg prednisone q d. Severe cases may necessitate treatment with 30-40 mg/d for several months.

Radiation treatment with 1000-2000 rads may be needed for cases of reactive lymphocytic hyperplasia.

TOLOSA-HUNT SYNDROME

Nonspecific inflammation in the region of the superior orbital fissure, often with extension into the cavernous sinus, sometimes with granulomatous features. A diagnosis of exclusion. May be a topographical variant of orbital pseudotumor (*see above*). Clinical diagnostic criteria:

1. painful ophthalmoplegia
2. involvement of any nerve traversing the cavernous sinus. The pupil is usually spared (frequently not the case with aneurysms, specific inflammation, etc.)
3. symptoms last days to weeks
4. spontaneous remission, sometimes with residual deficit
5. recurrent attacks with remissions of months or years
6. no systemic involvement (occasional N/V, due to pain?)
7. dramatic improvement with systemic steroids: 60-80 mg prednisone PO q day (slow taper), relief within about 1 day
8. occasional inflammation of rectus muscle from contiguous inflammation

RAEDER'S PARATRIGEMINAL NEURALGIA

Two essential components[15]:

1. unilateral oculosympathetic paresis (AKA partial Horner's syndrome **(HS)**, this usually lacks anhidrosis, and in this syndrome, possibly ptosis also)
2. homolateral trigeminal nerve involvement (usually tic-like pain, but may be analgesia or masseter weakness; pain, if present, must be tic-like and does not include e.g. unilateral head, face or vascular pain)

Localizing value of syndrome: region adjacent to trigeminal nerve in middle fossa. The cause is often not determined, but may rarely be due to aneurysm[16] compressing V_1 with sympathetics.

GRADENIGO'S SYNDROME

AKA apical petrositis. Mastoiditis with involvement of petrous apex (if pneumatized). Usually seen by ENT physicians. Classic triad:

1. abducens palsy: from inflammation of 6th nerve at Dorello's canal, which is where it enters the cavernous sinus just medial to the petrous apex
2. retro-orbital pain: due to inflammation of V_1
3. draining ear

25.6. Miscellaneous neurophthalmologic signs

Corneal mandibular reflex: eliciting the corneal reflex produces a jaw jerk or contralateral jaw movement (ipsilateral pterygoid contraction). A primitive pontine reflex, may be seen in a variety of insults to the brain (trauma, intracerebral hemorrhage…).

Duane syndrome: AKA retraction syndrome: paradoxical innervation causing co-contraction of the lateral and medial rectus muscles on attempted adduction with relaxation on abduction, produces mild enophthalmos with pseudoptosis. May be congenital (e.g. part of one of the following syndromes: acrorenal-ocular syndrome, Okihiro syndrome…).

Hippus: rhythmic, irregular pupillary oscillations, changing by ≥ 2 mm. May confuse examination when checking pupillary responses; record the initial response. May be normal. No localizing value.

Marcus Gunn phenomenon: not to be confused with Marcus Gunn *pupil* (*see page 831*). Opening the mouth causes opening of a ptotic eye (abnormal

reflex between prop-rioception of pterygoid muscles and third nerve). Reverse Marcus Gunn phenomenon: normal eye that closes with opening the mouth. Seen only in patients with peripheral facial nerve injuries, and probably results from aberrant regeneration.

Ocular bobbing[17]: abrupt, spontaneous, conjugate downward eye deviation with slow return to midposition, 2 to 12 times per min. It is associated with bilateral paralysis of horizontal gaze, including to doll's-eyes and calorics. Most commonly seen with destructive lesions of the pontine tegmentum (usually hemorrhage, but also infarction, glioma, trauma), but has also been described with compressive lesions[18]. Atypical bobbing is similar except that horizontal gaze is preserved, and can be seen with cerebellar hemorrhage, hydrocephalus, trauma, metabolic encephalopathy…

Opsoclonus[19]: (rare) rapid, conjugate, irregular, non-rhythmic (differentiates this from nystagmus) eye movements vertically or horizontally, persist (attenuated) during sleep (opsochoria if dysconjugate). Usually associated with diffuse myoclonus (fingers, chin, lips, eyelid, forehead, trunk and LEs); also, malaise, fatigability, vomiting and some cerebellar findings. Often resolves spontaneously within 4 mos.

Oscillopsia: visual sensation that stationary objects are swaying side-to-side or vibrating[20]. Rarely the sole manifestation of Chiari I malformation[21] (often associated with downbeat nystagmus). Other causes include MS, or injury to both vestibular nerves (e.g. aminoglycoside ototoxicity[22], bilateral vestibular neurectomies (see *Dandy's syndrome*, page 841)).

OPTIC ATROPHY

Chronic, progressive optic atrophy is due to a compressive lesion (aneurysm, meningioma, osteopetrosis…) until proven otherwise.

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26. Neurotology

26.1. Dizziness and vertigo

Differential diagnosis of dizziness:

1. near syncope: some overlap with syncope (see *Syncope and apoplexy*, page 1199)
   A. orthostatic hypotension
   B. cardiogenic hypotension
      1. arrhythmia
      2. valvular disease
   C. vasovagal episode
   D. hypersensitive carotid sinus: (see *Syncope and apoplexy*, page 1199)
2. dysequilibrium
   A. multiple sensory deficits: e.g. peripheral neuropathy, visual impairment
   B. cerebellar degeneration
3. <u>vertigo</u>: sensation of movement (usually spinning)
   A. inner ear dysfunction
      1. labyrinthitis
      2. Meniere's disease (*see below*)
      3. trauma: endolymphatic leak
      4. <u>drugs</u>: especially aminoglycosides
      5. **benign (paroxysmal) positional vertigo** [1]: AKA <u>cupulolithiasis</u>. Attacks of severe vertigo when the head is turned to certain positions (usually in bed). Due to calcium concretions in the semicircular canals. Self limited (most cases do not last > 1 year). No hearing loss
      6. syphilis
      7. vertebrobasilar insufficiency: *see page 1158*
   B. vestibular nerve dysfunction
      1. vestibular neuronitis: sudden onset of vertigo, gradual improvement

2. compression:
   a. meningioma
   b. vestibular schwannoma: usually slowly progressive ataxia instead of severe vertigo. BAER latencies usually abnormal. CT or MRI usually abnormal

C. **disabling positional vertigo**: as described by Jannetta et al.[2], constant disabling positional vertigo or dysequilibrium, causing ≈ constant nausea, no vestibular dysfunction nor hearing loss (tinnitus may be present). One possible cause is vascular compression of the vestibular nerve which may respond to microvascular decompression

D. brainstem dysfunction
   1. vascular disease (see *Vertebrobasilar insufficiency*, page 1158): less distinct vestibular symptoms, prominent nonvestibular symptoms
   2. migraine: especially basilar artery migraine
   3. demyelinating disease: e.g. multiple sclerosis
   4. drugs: anticonvulsants, alcohol, sedatives/hypnotics, salicylates

E. dysfunction of cervical proprioceptors: as in cervical osteoarthritis

4. poorly defined light-headedness: mostly psychiatric. May also include:
   A. hyperventilation
   B. hypoglycemia
   C. anxiety neurosis
   D. hysterical

VESTIBULAR NEURECTOMY

Complete loss of vestibular function from one side is thought to produce transient vertigo due to the mismatch of vestibular input from the two ears. Theoretically, a central compensatory mechanism (the "**cerebellar clamp**") results in the amelioration of symptoms. In cases of unilateral fluctuating vestibular dysfunction, this compensatory mechanism may be impaired. Unilateral selective vestibular neurectomy **(SVN)** may convert the fluctuating or partial loss to a complete cessation of input and facilitate compensation. Bilateral SVN is often complicated by oscillopsia (*see page 839*, AKA **Dandy's syndrome**, with difficulty in maintaining balance in the dark due to loss of the vestibulo-ocular reflex) and is to be avoided.

Indications

The two conditions for which SVN is most commonly employed are Meniere's disease (*see below*) and partial vestibular injury (viral or traumatic). SVN may be indicated in disabling cases refractory to medical or non-destructive surgical treatment when vestibular studies demonstrate continued or progressive uncompensated vestibular dysfunction[3].

SVN preserves hearing and in Meniere's disease is > 90% effective in eliminating episodic vertiginous spells (≈ 80% success rate in non-Meniere's cases), but is unlikely to improve stability with rapid head movement.

Surgical approaches for SVN

1. **retrolabyrinthine**, AKA postauricular approach: anterior to sigmoid sinus. Primary choice in patients with Meniere's disease who have not had previous endolymphatic sac **(ELS)** procedures since it permits simultaneous SVN and decompression of the endolymphatic sac. Requires mastoidectomy with skeletonization of the semicircular canals and ELS. The dural opening is bounded anteriorly by the posterior semicircular canal, posteriorly by the sigmoid sinus. Water-tight dural closure is difficult
2. **retrosigmoid**, AKA posterior fossa, AKA suboccipital approach: posterior to sigmoid sinus. The original approach plied by Dandy in pre-microsurgical era, usually sacrificed hearing, and occasionally facial nerve function. Better results today with microscopic techniques. Indicated for cases other than Meniere's disease where there is no need for identification of the ELS. Also the best approach for positive identification of eighth nerve
3. **middle fossa** (extradural) approach: the fibers of the vestibular division may be more segregated from the cochlear fibers in the IAC than in the CPA, thus permitting more complete section of the vestibular nerve. May be appropriate for failed response to SVN by the above approaches. Disadvantages: requires temporal lobe retraction, does not allow exposure of ELS, and higher morbidity and risk of damage to facial nerve[4] than retrolabyrinthine approach

Surgical considerations for selective vestibular neurectomy

(Also see *Figure 5-7*, page 90)

- the vestibular nerve is in the superior half of the eighth nerve complex, and is slightly more <u>gray</u> in color than the cochlear division (due to less myelin[5]). They may be separated by a small vessel or by an indentation in the bundle
- facial (VII) nerve:
  - whiter than the VIII nerve complex
  - lies anterior and superiorly to the VIII nerve
  - EMG monitoring of the facial nerve is recommended
  - direct stimulation confirms the identification
- any vessels present on eighth nerve bundle must be preserved to save hearing (primarily, the artery of the auditory canal must be preserved)
- if no plane of cleavage can be defined between vestibular & cochlear divisions, the superior half of the nerve bundle is divided
- the endolymphatic sac lies ≈ midway between the posterior edge of the internal auditory meatus and the sigmoid sinus

26.2. Meniere's disease

Key concepts:

> - increased endolymphatic pressure
> - clinical triad: vertigo, tinnitus & <u>fluctuating</u> hearing loss
> - surgical options for failure of medical management include endolymphatic shunt or selective vestibular neurectomy

Probably due to a derangement of endolymphatic fluid regulation (a consistent finding is **endolymphatic hydrops**: increased endolymphatic volume and pressure with dilatation of endolymph spaces), with resultant fistulization into the perilymphatic spaces.

CLINICAL

Clinical triad

- attacks of violent vertigo (due to vestibular nerve dysfunction): usually the earliest and the most disabling symptom. Nausea, vomiting, and diaphoresis

are frequent concomitants. Severe attacks may cause prostration. Vertigo may persist even after complete deafness. Balance is normal between attacks

- tinnitus: often described as resembling the sound of escaping steam, not a true “ringing”
- fluctuating low frequency hearing loss: may fluctuate for a periods of weeks to years, and may progress to permanent deafness if untreated (a sensation of fullness in the ear is commonly described[6], however, this is nonspecific and may occur with hearing loss for any reason)

Drop attacks (“otolithic crises of Tumarkin”) occasionally occur.

Attack duration: ≈ 5-30 minutes (some say 2-6 hours), with a “post-ictal” period of fatigue lasting several hrs.

Frequency: varies from one or two attacks a year to several times per week.

Two subtypes differ from classical form: vestibular Meniere’s (episodic vertigo with normal hearing) and cochlear Meniere’s (few vestibular symptoms).

Natural course of syndrome is characterized by periods of remission. Eventually the vertiginous attacks either progress in severity, or “burn out” (being replaced by constant unsteadiness[6]).

EPIDEMIOLOGY

Incidence ≈ 1 per 100,000 population[7]. Most cases have onset between 30-60 years of age, rarely in youth or in the elderly. May become bilateral in 20%.

DIFFERENTIAL DIAGNOSIS

(Also see *Differential diagnosis: Dizziness and vertigo* on page 840 for more details)

1. benign (paroxysmal) positional vertigo: AKA <u>cupulolithiasis</u>. Self limited (most cases last < 1 year). No hearing loss
2. disabling positional vertigo: <u>constant</u> disabling positional vertigo or dysequilibrium, ≈ constant nausea, no vestibular dysfunction nor hearing loss (tinnitus may be present)
3. vestibular schwannoma: usually slowly progressive ataxia instead of episodic severe vertigo. BAER latencies usually abnormal. CT or MRI usually positive
4. vestibular neuronitis: sudden onset of vertigo with gradual improvement
5. vertebrobasilar insufficiency **(VBI)**: less distinct vestibular symptoms, and prominence of nonvestibular symptoms (*see page 1158*)

DIAGNOSTIC STUDIES

1. electronystagmography **(ENG)** with bithermal caloric stimulation usually abnormal, may show blunted thermal responses
2. audiogram: low frequency hearing loss, fairly good preservation of discrimination and loudness recruitment, negative tone decay on impedance testing
3. BAER usually shows normal latencies
4. radiographic imaging (CT, MRI, etc.): no findings in Meniere's disease
5. in bilateral cases, a VDRL should be checked to R/O luetic disease

TREATMENT

MEDICAL TREATMENT

1. reduced intake of salt (strict salt restriction is as effective as any medication) and caffeine
2. diuretics: taken daily until ear fullness abates, then PRN ear pressure (usually once or twice weekly suffices)
   A. acetazolamide: ***Rx*** Diamox® sequels 500 mg p.o. q d **x** 1 week, increase to BID if symptoms persist. D/C if paresthesias develop. Do not use during 1st rimester of pregnancy
3. vestibular suppressants
   A. diazepam (Valium®): probably the most effective
   B. meclizine HCl (Antivert®): ***Rx*** Adult dose for vertigo associated with the vestibular system (during attacks): 25-100 mg/day PO divided. Dose for motion sickness: 25-50 mg PO one hr prior to stimulus. Supplied: 12.5, 25 & 50 mg tabs. **SIDE EFFECTS:** drowsiness
4. vasodilators: postulated to be mediated by increased cochlear blood flow: inhalation of 5-10% CO_2 works well, but relief is short lived

SURGICAL TREATMENT

Reserved for incapacitating cases refractory to medical management. When functional hearing exists, procedures that spare hearing are preferred because of high incidence of bilateral involvement. Procedures include:

1. endolymphatic shunting procedures: to mastoid cavity (Arenberg shunt) or to subarachnoid space. Reserved for cases with serviceable hearing. ≈ 65% success rate (*see below*). If symptoms are relieved ≥ 1 year, then a recurrence would be treated by shunt revision, if < 1 year then vestibular

neurectomy
2. direct application of corticosteroids to the inner ear
3. nonselective vestibular ablation (in cases with nonserviceable hearing on the side of involvement)
   A. surgical labyrinthectomy
   B. middle ear perfusion with gentamicin
   C. translabyrinthine section of the 8th nerve
4. selective vestibular neurectomy (in cases with serviceable hearing): *see page 840*

OUTCOME

ENDOLYMPH SHUNTING PROCEDURES

Outcomes from 112 endolymphatic shunting procedures are shown in *Table 26-1*.

NEURECTOMY PROCEDURES

Vestibulocochlear nerve section (based on early posterior fossa surgery by Dandy; entire eighth nerve bundle was sectioned in 587 patients; all were deaf post-op): 90% relieved of vertigo, 5% unchanged and 5% worse; 9% incidence of facial paralysis (3% incidence of permanent paralysis).

Selective vestibular nerve section (sparing cochlear portion, 95 patients from Dandy): 10% had improved hearing, 28% unchanged, 48% worse, 14% deaf.

Retrolabyrinthine approach: in 32 patients with Meniere's syndrome (25 failed endolymph shunt) responding to survey, 85% had complete relief of vertigo, 6% improved, 9% no relief (one of whom responded to middle fossa neurectomy)[5].

Table 26-1 Outcome*[6]

	Vertigo	Tinnitus	Hearing†	Ear pressure
improved	79 (70%)‡	53 (47%)	19 (17%)	57 (51%)
stable	33 (29%)	49 (43%)	50 (45%)	24 (21%)
worse	(none)	10 (10%)	39 (35%)	31 (28%)

* in 112 endolymphatic-subarachnoid shunts

† improved hearing considered serviceable (50 dB pure tone, 70% speech discrimination); additional 4 patients had improved but non-serviceable hearing

‡ 5 patients had recurrence of vertigo after 1-3 years

Complications and untoward effects

Patients with little vestibular nerve function pre-op (determined by ENG) usually have little difficulty immediately following vestibular neurectomy; patients with more function may have a transient worsening post-op until they accommodate.

Among 42 patients undergoing retrolabyrinthine approach: none lost hearing as a result of surgery, no facial weakness, one CSF rhinorrhea requiring re-operation, and one meningitis with good outcome[5].

In post-op failures, check ENG. If any vestibular nerve function is demonstrated on operated side, then the nerve section was incomplete; consider re-operating.

26.3. Facial nerve palsy

Severity of facial palsy is graded with the House and Brackmann scale (see *Table 21-27*, page 622).

LOCALIZING SITE OF LESION

Central facial palsy (AKA supranuclear facial palsy)

The cortical representation for facial movement occurs in the motor strip along the lateral aspect (just above the most inferior opercular portion of the precentral gyrus). The keys to differentiating central paralysis (due to supranuclear lesions) from peripheral facial palsy are that central palsies:

1. are confined primarily to the lower face due to some bilateral cortical representation of upper facial movement
2. may spare emotional facial expression[8] (e.g. smiling at a joke)

Nuclear facial palsy

The motor nucleus of the seventh nerve is located at the pontomedullary junction. Nuclear VII palsy results in paralysis of all VII nerve motor function. In nuclear facial palsies, other neurologic findings also often occur from involvement of adjacent neural structures by the underlying process (stroke, tumor…), e.g. in Millard-Gubler syndrome, there is ipsilateral abducens palsy +

contralateral limb weakness (*see page 114*). Tumors invading the floor of the 4th ventricle (e.g. medulloblastoma) may also cause nuclear facial palsy (from involvement of facial colliculus in the floor of 4th ventricle).

Facial nerve lesion

Motor fibers ascend within the pons and form a sharp bend ("**internal genu**") around the sixth nerve (abducens) nucleus, forming a visible bump in the floor of the 4th ventricle (**facial colliculus**). The seventh nerve exits from the brain stem at the pontomedullary junction (see *Figure 5-20*, page 102) where it may be involved in CPA tumors. It enters the supero-anterior portion of the internal auditory canal (see *Figure 5-7*, page 90). The geniculate ganglion ("**external genu**") is located within the temporal bone. The first branch from the ganglion is the greater superficial petrosal nerve **(GSPN)** which passes to the pterygopalatine ganglion and innervates the nasal and palatine mucosa and the lacrimal gland of the eye; lesions proximal to this point produce a dry eye. The next branch is the branch to the stapedius muscle; lesions proximal to this point produce hyperacusis. Next, the chorda tympani joins the facial nerve bringing taste sensation from the anterior two thirds of the tongue. Basal skull fractures may injure the nerve just proximal to this point. Travelling with the chorda tympani are fibers to the submandibular and sublingual glands. The facial nerve exits the skull at the stylomastoid foramen. It then enters the parotid gland, where it splits into the following branches to the facial muscles (cranial to caudal): temporal, zygomatic, buccal, mandibular, and cervical. Lesions within the parotid gland (e.g. parotid tumors) may involve some branches but spare others.

ETIOLOGIES

These etiologies produce primarily facial nerve palsy, also see *Multiple cranial nerve palsies (cranial neuropathies)*, page 1202.

1. Bell's palsy: *see below* } 90-95% of all cases of facial palsy[9]
2. herpes zoster oticus (auris): *see page 846* } 90-95% of all cases of facial palsy[9]
3. trauma: basal skull fracture } 90-95% of all cases of facial palsy[9]
4. birth:
   A. congenital
      1. *bilateral facial palsy (facial diplegia) of Möbius syndrome: unique in that it affects upper face more than lower face (*see page*

1202)

2. *congenital facial diplegia may be part of facioscapulohumeral or myotonic muscular dystrophy

B. traumatic

5. otitis media: with acute otitis media, facial palsy usually improves with antibiotics. With chronic suppurative otitis surgical intervention is required
6. central facial paralysis and nuclear facial paralysis: see *Localizing site of lesion* above
7. neoplasm: usually causes hearing loss, and (unlike Bell's palsy) slowly progressive facial paralysis
   A. most are either benign schwannomas of the facial or auditory nerve, or malignancies metastatic to the temporal bone. Facial neuromas account for ≈ 5% of peripheral facial nerve palsies[10]; the paralysis tends to be slowly progressive (*see page 1210*)
   B. parotid tumors may involve some branches but spare others
   C. Masson's vegetant intravascular hemangioendothelioma (*see page 716*)
8. *neurosarcoidosis: VII is the most commonly affected cranial nerve (*see page 71*)
9. diabetes: 17% of patients > 40 yrs old with peripheral facial palsy **(PFP)** have abnormal glucose tolerance tests. Diabetics have 4.5 times the relative risk of developing PFP than nondiabetics[11]
10. *stage II Lyme disease[12] (*see page 368*): facial diplegia is a hallmark
11. *Guillain-Barré syndrome: facial diplegia occurs in ≈ 50% of fatal cases
12. occasionally seen in Klippel-Feil syndrome
13. *isolated 4th ventricle (*see page 309*): compression at the facial colliculus

* items with an asterisk are often associated with facial diplegia (i.e. bilateral facial palsy), for multiple cranial neuropathies *see page 1202*

BELL'S PALSY

Bell's palsy **(BP)**, AKA idiopathic peripheral facial palsy **(PFP)**, is the most common cause of facial paralysis (50-80% of PFPs). Incidence: 150-200/1-million/yr.

Etiology: by definition, PFP is called Bell's palsy when it is not due to known causes of PFP (e.g. infection, tumor or trauma) and there are no other neurological (e.g. involvement of other cranial nerves) or systemic

manifestations (e.g. fever, diabetes, possibly hypertension[13])[14]. Thus, true BP is idiopathic, and is a diagnosis of exclusion. Most cases probably represent a viral inflammatory demyelinating polyneuritis[15] usually due to the herpes simplex virus[16]. Facial palsy due to Lyme disease can usually be recognized on clinical grounds[17]. Severity may be graded on the House & Brackmann grading scale (see *Table 21-27*, page 622).

Presentation

A viral prodrome is frequent: URI, myalgia, hypesthesia or dysesthesia of the trigeminal nerve, N/V, diarrhea… Paralysis may be incomplete and remain so (Type I); it is complete at onset in 50% (Type II), the remainder progress to completion in 1 week. Usually exhibits distal to proximal progression: motor branches, then chorda tympani (loss of taste and decreased salivation), then stapedial branch (hyperacusis), then geniculate ganglion (decreased tearing). Associated symptoms are shown in *Table 26-2*, and are usually, but not always, ipsilateral. Herpes zoster vesicles develop in 4% of patients 2-4 days after onset of paralysis; and in 30% of patients 4-8 days after onset. During the recovery phase excessive lacrimation may occur (aberrant nerve regeneration).

Table 26-2 Associated symptoms with Bell's palsy

Symptom	%
facial & retroauricular pain	60%
dysgeusia	57%
hyperacusis	30%
reduced tearing	17%

Prognosis

All cases show some recovery (if none by 6 mos, other etiologies should be sought). Extent of recovery: 75-80% of cases recover completely, 10% partial, remainder poor. If recovery begins by 10-21 d, tends to be complete; if not until 3-8 wks → fair, if not until 2-4 mos → poor recovery. If paralysis is complete at onset, 50% will have incomplete recovery. Cases of incomplete paralysis at onset that do not progress to complete paralysis → complete recovery; incomplete paralysis at onset that progresses to complete → incomplete recovery in 75%. A worse prognosis is associated with: more proximal involvement, hyperacusis, decreased tearing, age > 60 yrs, diabetes, HTN, psychoneuroses, and aural, facial or radicular pain.

Management

Patients with PFP should be examined at an early stage to optimize outcome.

Electrodiagnostics: EMG may detect re-innervation potentials, aids prognostication. Nerve conduction study: electrical stimulation of the facial nerve near the stylomastoid foramen while recording EMG in facial muscles (a facial nerve may continue to conduct for up to ≈ 1 week even after complete transection).

Eye protection: protection of the eye is critical. Artificial tears during the day, eye ointment at night, avoid bright light (using dark glasses during the day).

Steroids: prednisolone 25 mg p.o. BID **x** 10 days, started within 72 hours of onset of symptoms, improves the chances of complete recovery at 3 & 9 months.

Acyclovir: does <u>not</u> help (alone or in combination with prednisolone)[18].

Surgical decompression: controversial. The definitive study has not been done. Rarely utilized. Indications may include:

1. complete facial nerve degeneration without response to nerve stimulation (although this absence is also used as an argument against surgery[9])
2. progressively deteriorating response to nerve stimulation
3. no clinical nor objective (nerve testing) improvement after 8 wks (however, in cases where the diagnosis of Bell's palsy is felt to be certain, the active disease will have abated by ≈ 14 days after onset[9])

HERPES ZOSTER OTICUS FACIAL PARALYSIS

Symptoms are more severe than Bell's palsy, herpetic vesicles are usually present, and antibody titers to varicella-zoster virus rise. These patients have a higher risk of facial nerve degeneration.

SURGICAL TREATMENT OF FACIAL PALSY

For cases with focal injury to the facial nerve (e.g. trauma, injury during surgery for CPA tumor…), dynamic reconstruction by nerve anastomoses are usually considered superior to static methods[19]. For nonfocal causes, e.g. Bell's palsy, only "static" methods may be applicable. A functional neural repair is not possible if the facial muscles have atrophied or fibrosed.

Surgical treatment options include:

1. for intracranial injury to facial nerve (e.g. during CPA tumor surgery): intracranial reapproximation (with or without graft) offers the best hope for the most normal facial reanimation

A. timing
   1. at time of tumor removal (for a divided facial nerve during removal of vestibular schwannoma[20-22]): the best result that can be achieved with this is House-Brackmann Grade III. The operation fails to produce good results in ≈ 33% of cases[22]
   2. in delayed fashion, especially if the nerve was left in anatomic continuity

B. techniques
   1. direct reanastomosis: difficult due to the frail nature of the VII nerve (especially when it has been stretched by a tumor)
   2. cable graft: e.g. using greater auricular nerve[23] or sural nerve

2. extracranial facial nerve anastomosis
   A. hypoglossal nerve (Cr. N. XII)-facial nerve anastomosis: (*see below*)
   B. spinal accessory nerve (Cr. N. XI)-facial nerve anastomosis: (*see below*)
   C. phrenic nerve-facial nerve anastomosis
   D. glossopharyngeal (Cr. N. IX)-facial nerve anastomosis
   E. crossface grafting (VII-VII): results have not been very good
3. "mechanical" or "static" means
   A. facial suspension: e.g. with polypropylene (Marlex®) mesh[24]
   B. eye closure techniques (protects the eye from exposure and reduced tearing)
      1. tarsorrhaphy: partial or complete
      2. gold weights in eyelid
      3. stainless-steel spring in eyelid

Timing of surgery

If the facial nerve is known to be interrupted (e.g. transected during removal of vestibular schwannoma) then early surgical treatment is indicated. When the status of the nerve is unknown or if in continuity but not functioning, then several months of observation and electrical testing should be allowed for spontaneous recovery. Very late attempts at anastomosis have less chance for recovery due to facial muscle atrophy.

Hypoglossal nerve-facial nerve (XII-VII) anastomosis

Cannot be used bilateral in patients with facial diplegia or in those with other lower cranial nerve deficits (or potential for same). In spite of some suggestions

to the contrary, sacrificing the XII nerve does create some morbidity (tongue atrophy with difficulty speaking, mastication and swallowing in ≈ 25% of cases, exacerbated when the facial muscles do not function on that side; aspiration may occur if vagus (Cr. N. X) dysfunction coexists with loss of XII).

Not as effective as it would theoretically seem possible. The resultant facial reanimation is often less than ideal (may permit mass movement). To avoid severe disappointment, the patient should thoroughly understand the likely side effects and that the facial movement will probably be much less than normal, often with poor voluntary control.

Usually performed in conjunction with anastomosis of the descendens hypoglossi to the distal hypoglossal nerve to try and reduce hemiatrophy of the tongue. Atrophy may also be reduced by using a “jump graft” without completely interrupting XII[25].

Technique

Position: supine, head turned slightly to the opposite side. Skin incision: 6-8 cm incision from just above the mastoid process obliquely downward across the neck to 2 cm below the angle of the jaw. The platysma is opened, and the tip of the mastoid is exposed by incising the insertion of the SCM and using a periosteal elevator. Incise the deep fascia; avoid the parotid gland, which is retracted superiorly. Rongeur the anterior third of the mastoid process (wax any exposed air cells) and identify the facial nerve as it exits the stylomastoid foramen between the mastoid process and the styloid process. Retract the posterior belly of the digastric inferiorly to aid the exposure.

The SCM is retracted laterally until the carotid sheath is identified, revealing the hypoglossal nerve. It loops around the occipital artery at this level (where it gives off the descendens hypoglossi) to pass between the carotid artery and jugular vein. The nerve is freed proximally to the point where it enters the carotid sheath and distally to the submandibular triangle where it is sharply divided.

The facial nerve is divided at the stylomastoid foramen and is approximated to the proximal hypoglossal nerve. The descendens hypoglossi is divided as far distally as possible and is then anastomosed to the distal stump of the hypoglossal nerve.

Variations:

1. interposition jump grafts: spares function in the XII nerve (to minimize glottic denervation, the incision of XII should be distal to the descendens

hypoglossi[25])

   A. using cutaneous nerve jump graft[25]

   B. using muscle interposition jump graft[26]

2. mobilizing the infratemporal portion of VII out of the fallopian canal (as previously described[27]) and then anastomosing it using a bevelled cuts to a partially incised XII[28]

Outcome

Results are better if performed early, although good results can occur up to 18 mos after injury. In 22 cases, 64% had good results, 14% fair, 18% poor, and 1 patient had no evidence of reinnervation. In 59% of cases, evidence of reinnervation was seen by 3-6 mos, in the remaining patients with reinnervation improvement was noted by 8 mos[29]. Recovery of forehead movement occurs in only ≈ 30%. Return of tone precedes movement by ≈ 3 months.

Spinal accessory nerve-facial nerve (XI-VII) anastomosis

First described in 1895 by Sir Charles Ballance[30]. Sacrifices some shoulder movement rather than use of tongue. Initial concerns about significant shoulder disability and pain resulted in the technique of using only the SCM branch of XI[31], however these problems have not occurred in the majority of patients even with use of the major division[32].

Technique[32]

Skin incision: curves across the mastoid tip along the anterior margin of the SCM. Strip and remove the anterior third of the mastoid process (wax any exposed air cells), identify the facial nerve and divide it as close to its exit from the stylomastoid foramen as possible. Locate the XI nerve 3-4 cm below the mastoid tip, and divide it distal to the SCM division. Mobilize the free end and anastamose it to the distal stump of VII. Results in loss of trapezius function, which may not cause deficit even if done bilaterally. Alternatively, the SCM branch of XI may be used, sparing the trapezius function, however the shorter length may be difficult to work with and in some individuals there may only be multiple small branches to the SCM.

26.4. Hearing loss

Two anatomic types: conductive and sensorineural.

1. **conductive** hearing loss
   A. patients tend to speak with normal or low volume voice
   B. etiologies: anything that interferes with ossicular movement, including: otitis media with middle ear effusion, otosclerosis
   C. clinical findings with unilateral hearing loss (*see Table 26-3*):
      1. Weber test[A] will lateralize to side of hearing loss
      2. Rinne test[B] will be abnormal (BC > AC) on the side of hearing loss, called a negative Rinne
   D. middle ear impedance measurements are abnormal
2. **sensorineural** hearing loss **(SNHL)**
   A. patients tend to speak with loud voice
   B. clinical findings with unilateral hearing loss (*see Table 26-3*):
      1. Weber test[A] will lateralize to side of better hearing
      2. Rinne test[B] will be normal (AC > BC), called a positive Rinne
   C. further divided into sensory or neural. Distinguished by otoacoustic emissions (only produced by a cochlea with functioning hair cells) or BSAERs
      1. sensory: loss of outer hair cells in the cochlea. Etiologies: cochlear damage (usually causes high-frequency hearing loss) from noise exposure, ototoxic drugs (e.g. aminoglycosides), senile cochlear degeneration, viral labyrinthitis. Speech discrimination may be relatively preserved
      2. neural: due to compression of the 8th cranial nerve. Etiologies: CP angle tumor (e.g. vestibular schwannoma). Typically loss of word discrimination out of proportion to pure tone audiogram abnormalities
   - Sensory and neural hearing loss may be distinguished by otoacoustic emissions (only produced by a cochlea with functioning hair cells) or BSAERs. An elevated stapedial reflex threshold out of proportion to PTA abnormalities is also highly diagnostic of a retrocochlear (neural) lesion

Table 26-3 Interpretation of Weber and Rinne test results

Weber	Rinne	Interpretation
nonlateralizing	AC > BC bilat	normal*

lateralizes to side A	normal bilaterally (AC > BC)	sensorineural hearing loss (SNHL) side B
lateralizes to side A	abnormal in side A (BC > AC)	conductive hearing loss side A
lateralizes to side A	abnormal in side B (BC > AC)	combined conductive + SNHL side B

* normal, or symmetric hearing loss

A. Weber test: place a vibrating 256 or 512 Hz tuning fork on the center of the forehead. The sound will lateralize (sound louder) on the side of conductive hearing loss, or opposite to the side of SNHL
B. Rinne test: place a vibrating 256 or 512 Hz tuning fork on the mastoid process, when sound is no longer heard, move the fork to just outside the ear to see if air conduction **(AC)** is > bone conduction **(BC)**

26.5. References

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27. Head trauma

CONCUSSION

AKA mild traumatic brain injury **(MTBI)**.

Definition: Alteration of consciousness without structural damage as a result of nonpenetrating traumatic brain injury **(TBI)**. Alterations in consciousness may include: confusion, amnesia (the hallmarks of concussion), or loss of consciousness **(LOC)**. *Loss* of consciousness is <u>not</u> a requirement[1-4] (*see Table 27-2* for grading scales). Frequent neurobehavioral features of concussion are shown in *Table 27-1*. Patients themselves may be unaware whether or not they experienced LOC[5].

The alteration should be "brief", but there is no consensus on the length of time considered to be "brief".

There are no gross or microscopic parenchymal abnormalities. CT is normal or significant only for mild swelling which may represent hyperemia[6]. MRI will demonstrate abnormalities in up to 25% of cases where CT is normal[7]. The term *contusion* should be used when there are structural abnormalities (as may be seen on CT).

Confusion may be evident immediately following the blow, or may take several minutes to develop[8]. When there is LOC, the fact that it is often virtually instantaneous (there may be a latency of a few seconds), and the usually rapid return of function with no evidence of microscopic changes suggests that the LOC is due to a transient disturbance in neuronal function. Levels of glutamate (an excitatory neurotransmitter) rise after concussion and the brain enters a hyperglycolytic and hypermetabolic state which may persist up to 7-10 days after the injury. During this period the brain may be more susceptible to a second insult (second impact syndrome, *see below*) which, due in part to impairment of cerebral autoregulation, may produce much more severe sequelae (including possible malignant cerebral edema, *see page 852*) than it would have acting alone.

Also, *see below* for sports-related concussion.

Concussion may be followed by post-concussive syndrome (*see page 910*).

Table 27-1 Possible findings in concussion[1]

- vacant stare or befuddled expression
- delayed verbal & motor responses: slow to answer questions or follow instructions
- easy distractibility, difficulty focusing attention, inability to perform normal activities
- disorientation: walking in the wrong direction, unaware of date, time or place
- speech alterations: slurred or incoherent, disjointed or incomprehensible statements
- incoordination: stumbling, inability to tandem walk
- exaggerated emotionality: inappropriate crying, distraught appearance
- memory deficits: repeatedly asking same question that has been answered, cannot name 3 out of 3 objects after 5 minutes
- any period of LOC: paralytic coma, unresponsiveness to stimuli

Management and admission criteria

See Categories 1 & 2 on *page 856*.

SPORTS RELATED CONCUSSION

≈ 10% of head and spinal injuries are a result of a sports-related event[9]. Concussion, AKA mild traumatic brain injury **(MTBI)**, is very different from the severe types of head injuries commonly seen by neurosurgeons in the E/R and office. The widest experience in studying this entity derives from athletics, and generalization to other types of trauma must be done circumspectly.

Concussion grading

The Glasgow coma scale is too insensitive for use with mild TBI. Many concussion grading systems have been proposed, the two most widely used are those of Cantu[10, 11], and that of the American Academy of Neurology **(AAN)**[4] (based on the guidelines of the Colorado Medical Society[12]) both of which are shown in *Table 27-2*. LOC by itself may not be a significant discriminant (e.g. confusion > 30 minutes may be worse than LOC for a few seconds). Most systems consider a concussion to be mild if there is a change in sensorium without loss of consciousness, however they differ mostly in the definition of "change in sensorium".

There is no scientific basis to recommend one system over another. Recommendation: select one system and use it consistently. Do not place undue emphasis on grading

Second impact syndrome (SIS)

A rare condition described primarily in athletes who sustain a second head injury while still symptomatic from an earlier one. Classically, the athlete walks

off the field under their own power after the second injury, only to deteriorate to coma within 1-5 minutes and then, due to vascular engorgement, develops malignant cerebral edema that is refractory to all treatment and progresses to herniation. Mortality: 50-100%.

A syndrome compatible with SIS was first described by Schneider[13] in 1973, and was later dubbed the “second impact syndrome of catastrophic head injury” in 198414. Although it is contended that SIS is rare (if it exists at all) and may be overdiagnosed[15], its apparent predilection for teens and children still warrants extra precaution following concussion.

Table 27-2 Concussion grading

Grade	Cantu system*	★ AAN system*
1 (mild)	1. PTA < 30 mins 2. no LOC	1. transient confusion 2. no LOC 3. symptoms resolve in < 15 mins
2 (moderate)	1. LOC < 5 mins, or 2. PTA > 30 mins	as above, but symptoms last > 15 mins (still <u>no</u> LOC) (PTA is common)
3 (severe)	1. LOC ≥ 5 mins, or 2. PTA ≥ 24 hrs	<u>any</u> LOC

* abbreviations: LOC = loss of consciousness; PTA = posttraumatic amnesia

Return to play guidelines

No system of return to play **(RTP)** guidelines has been rigorously tested and proven to be scientifically sound. Regardless of the system used, one universal recommendation of experts is:

★ <u>a symptomatic player should not return to competition</u>.

PRACTICE GUIDELINE 27-1 shows AAN guidelines for RTP (if no contraindications, *see Table 27-3*[16]). For spine-related RTP guidelines, *see page 980*.

Table 27-3 Cerebral contraindications for return to contact sports

1. persistent postconcussion symptoms
2. permanent CNS sequelae from head injury (e.g. organic dementia, hemiplegia, homonymous hemianopsia)
3. hydrocephalus
4. spontaneous SAH from any cause
5. symptomatic (neurologic or pain producing) abnormalities about the foramen magnum (e.g. Chiari

malformation)

PRACTICE GUIDELINE 27-1 SPORTS RELATED CONCUSSION	
Level III[4] AAN guidelines:	
AAN grade	**Management recommendations for a single sports-related concussion (level III recommendations)**
1 mild	1. remove from contest 2. examine q 5 mins for amnesia or postconcussive symptoms* 3. may return to contest if symptoms clear within 15 mins
2 moderate	1. remove from contest 2. disallow return that day 3. examine on-site frequently for signs of evolving intracranial pathology 4. reexamination the next day by a trained individual 5. CT or MRI if H/A or other symptoms worsen or last > 1 week† 6. return to practice after 1 full week without symptoms*
3 severe	1. ambulance transport from field to E/R if still unconscious or for concerning signs (C-spine precautions if indicated) 2. emergent neuro exam. Neuroimaging as appropriate 3. may go home with head-injury instructions (see *Table 27-10*, page 857) if normal findings at time of initial neuro exam 4. admit to hospital for any signs of pathology or for continued abnormal mental status 5. assess neuro status daily until all symptoms have stabilized or resolved 6. prolonged unconsciousness, persistent mental status alterations, worsening post-concussion symptoms, or abnormalities on neurologic exam → urgent neurosurgical evaluation or transfer to a trauma center 7. after brief (< 1 minute) grade 3 concussion, do not return to practice until asymptomatic for 1 full week* 8. after prolonged (> 1 minute) grade 3 concussion, return to practice only after 2 full weeks without symptoms*‡ 9. CT or MRI if H/A or other symptoms worsen or last > 1 week†

* evaluation at rest and with exertion (see text)

† season is terminated for that player if CT/MRI shows edema, contusion, or other acute intracranial pathology. Return to play in any contact sports in the future should be seriously discouraged

‡ some experts also require a normal CT scan

The rationale for the waiting periods following grade 2 or 3 concussions is due to the potentially increased vulnerability of the brain to injury following a concussion (see *Second impact syndrome*, page 851). Almost all players with mild concussions should be able to return to the contest. Some also allow players with moderate concussions to return if they become symptom-free at rest and with exertion using provocative tests. **Exertion**: to evaluate under exertion, commonly utilized provocative tests include the 40-yard run, sit-ups, push-ups, and/or deep knee-bends[9]. In the E/R, exertion may be administered by having the patient lie on the exam table and tip the head backward slightly off the edge. The development of any symptoms during exertion is considered abnormal and precludes return to the present contest.

Multiple concussions: Multiple concussions in a short period of time are potentially dangerous (*see above*). Recommendations[9] for multiple concussions in the same season are shown in *Table 27-4*. Also, see *Chronic traumatic*

encephalopathy, page 911 for long-term effects of multiple concussions.

Neuroimaging

The need for neuroimaging (e.g. CT scan) in the athlete with resolved or improving symptoms is controversial, and is felt to be best left to the judgement of the treating physician. Suggested indications:

1. a severe concussion
2. symptoms persisting > 1 week, even if mild
3. before returning to competition after a 2nd or 3rd concussion in the same season

Table 27-4 Recommendations for multiple sports-related concussions in the same season

Concussion		Guidelines to be met before return to competition
No.	Severity	
2	mild	1 week*
	moderate or severe	1 month* + normal CT or MRI†
3	mild	most consider this a season ending injury and recommend CT or MRI†
	moderate	season ending injury, consideration for ending all participation in contact sports
2	severe	

* without symptoms at rest and with exertion (see text)

† if any acute abnormalities on CT/MRI: terminate season. Consider ending all participation in contact sports

CONTUSION

TBI with CT findings that may include:

- low attenuation areas: representing associated edema
- high attenuation areas (AKA "hemorrhagic contusions"): usually produce less mass effect than their apparent size. Most common in areas where sudden deceleration of the head causes the brain to impact on bony prominences (e.g. temporal, frontal and occipital poles). These areas may progress (or "blossom" in neuroradiological jargon) to frank parenchymal hemorrhages. Surgical decompression may sometimes be considered if herniation threatens (*see page 893*)

Contrecoup injury

(French: “counter blow”) in addition to the potential injury to the brain directly under the point of impact, the force imparted to the head may cause the brain to be thrust against the skull directly opposite the blow. May result in contusions typically in locations described above.

OTHER DEFINITIONS

Posttraumatic brain swelling

This term encompasses two distinct processes:

1. increased cerebral blood volume: may result from loss of cerebral vascular autoregulation (*see page 866*). This hyperemia may sometimes occur with extreme rapidity, in which case it has sometimes been referred to as diffuse or “**malignant cerebral edema**”[17] which carries close to 100% mortality and may be more common in children. Management consists of aggressive measures to maintain ICP < 20 mm Hg and CPP > 60 mm Hg[18A]
2. true cerebral edema: classically at autopsy these brains “weep fluid”[19]. Both vasogenic and cytotoxic cerebral edema (*see page 109*) can occur within hours of head injury[19, 20] and occasionally may be treated with decompressive craniectomy (see *PRACTICE GUIDELINE 27-21*, page 893)

Diffuse axonal injury (DAI) (AKA diffuse axonal shearing)

A primary lesion of rotational acceleration/deceleration head injury[21]. In its severe form, hemorrhagic foci occur in the corpus callosum and dorsolateral rostral brain stem with microscopic evidence of diffuse injury to axons (axonal retraction balls, microglial stars, and degeneration of white matter fiber tracts). Often cited as the cause of loss of consciousness in patients rendered immediately comatose following head injury in the absence of a space occupying lesion on CT[22] (although DAI may also be present with subdural[23] or epidural hematomas[24]).

May be diagnosed clinically when loss of consciousness (coma) lasts > 6 hours in absence of evidence of intracranial mass or ischemia. May be graded as shown in *Table 27-5*.

Table 27-5 Grading DAI

DAI grade	Description
mild	coma > 6-24 hrs, followed by mild-to-moderate memory impairment, mild-to-moderate disabilities
moderate	coma > 24 hrs, followed by confusion & long-lasting amnesia. Mild-to-severe memory, behavioral and cognitive deficits
severe	coma lasting months with flexor and extensor posturing. Cognitive, memory, speech, sensorimotor and personality deficits. Dysautonomia may occur

GRADING HEAD INJURIES

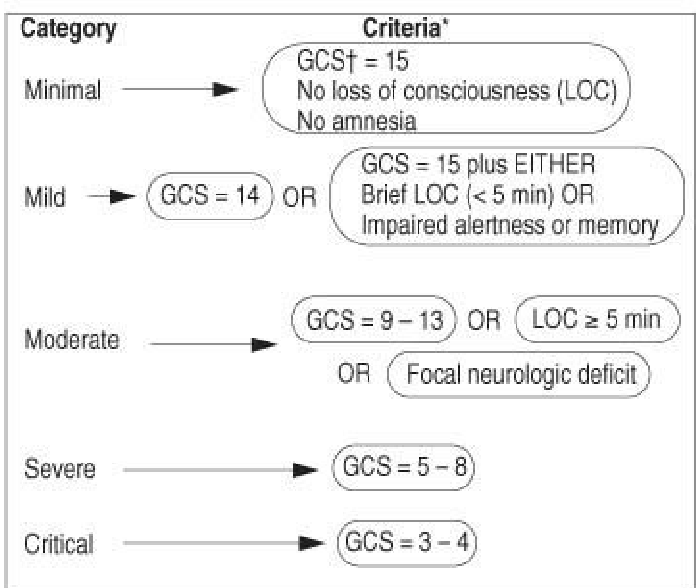
Despite many (valid) criticisms, the initial post-resuscitation Glasgow Coma Scale **(GCS)** score (see *Table 12-1*, page 279) remains the most widely used and perhaps best replicated scale employed in the assessment of head trauma.

Stratification: There are a number schemes to stratify the *severity* of head injury. Any such categorization is arbitrary. A simple system based only on GCS score is as follows: GCS 14–15 = mild, GCS 9–13 = moderate, and GCS ≤ 8 = severe.

A more involved system[25] incorporates other factors in addition to the GCS score as shown in *Table 27-6*.

A classification system based on CT scan[26] is shown in *Table 27-7*.

Table 27-6 Categorization of head injury severity



* ALL criteria in any oval must be met to qualify

† GCS = Glasgow coma scale (see *Table 12-1*, page 279)

GENERAL

56-60% of patients with GCS score ≤ 8 have 1 or more other organ system injured[27]. 25% have “surgical” lesions. There is a 4-5% incidence of associated spine fractures with significant head injury (mostly C1 to C3).

A. CPP ≥ 70 mm Hg is generally recommended (see *ICP treatment threshold*, page 876)

When a detailed history is unavailable, remember: the loss of consciousness may have preceded (and possibly have caused) the trauma. Therefore, maintain an index of suspicion for e.g. aneurysmal SAH, hypoglycemia, etc. in the differential diagnosis of the causes of trauma and associated coma.

Brain injury from trauma results from two distinct processes:

1. primary brain injury: occurs at time of trauma (cortical contusions, lacerations, bone fragmentation, diffuse axonal injury, and brainstem contusion)
2. secondary injury: develops subsequent to the initial injury. Includes injuries from intracranial hematomas, edema, hypoxemia, ischemia (primarily due to elevated intracranial pressure **(ICP)** and/or shock), vasospasm

Table 27-7 CT classification of head injury

Category	Definition	Mortality
Diffuse Injury I	no visible intracranial abnormality	10%
Diffuse Injury II	basal cisterns* present, 0-5 mm midline shift and/or lesion densities present	14%
Diffuse Injury III	basal cisterns* compressed or absent, 0-5 mm midline shift, no high or mixed density lesion > 25 cc	34%
Diffuse Injury IV	midline shift > 5 mm, no high or mixed density lesion > 25 cc	56%

* see page 909 for information on basal cisterns

Hypotension: Hypotension[A] (shock) is rarely attributable to head injury except:

A. SBP < 90 mm Hg may impair CBF and exacerbate brain injury and should be avoided *see page 878*

1. in terminal stages (i.e. with dysfunction of medulla and cardiovascular collapse)
2. in infancy, where enough blood can be lost intracranially or into the subgaleal space to cause shock
3. where enough blood has been lost from scalp wounds to cause hypovolemia

DELAYED DETERIORATION

≈ 15% of patients who do not initially exhibit signs of significant brain injury may deteriorate in a delayed fashion, sometimes referred to as patients who "talk and deteriorate" or when more lethal, patient who "**talk and die**"[28]. Etiologies:

1. ≈ 75% will exhibit an intracranial hematoma
    A. may be present on initial evaluation and can then worsen
    B. may develop in a delayed fashion
        1. delayed epidural hematoma **(EDH)**: *see page 896*
        2. delayed subdural **(SDH)**: *see page 899*
        3. delayed traumatic contusions: *see page 893*
2. posttraumatic diffuse cerebral edema: *see page 853*
3. hydrocephalus
4. tension pneumocephalus
5. seizures
6. metabolic abnormalities, includes:
    A. hyponatremia
    B. hypoxia: etiologies include pneumothorax, MI, CHF…
    C. hepatic encephalopathy
    D. hypoglycemia: including insulin reaction
    E. adrenal insufficiency
    F. drug or alcohol withdrawal
7. vascular events
    A. dural sinus thrombosis: *see page 1166*
    B. carotid (or rarely, vertebral) artery dissection: *see page 1163*
    C. SAH: due to rupture of aneurysm (spontaneous or posttraumatic) or carotid-cavernous fistula **(CCF)** (*see page 1113*)
    D. cerebral embolism: including fat embolism syndrome
8. meningitis

9. hypotension (shock)

27.1. Transfer of trauma patients

It is sometimes necessary for a neurosurgeon to accept a trauma patient in transfer from another institution that is not equipped to handle major neurologic injuries, or to transfer patients to other facilities for a variety of reasons. *Table 27-8* lists factors that should be assessed and stabilized (if possible) prior to transfer. These items should also be evaluated in trauma patients on whom a neurosurgeon is consulted in his or her own E/R as well as in patients with other CNS abnormalities besides trauma (e.g. SAH).

Table 27-8 Factors to assess in head injured patients

Clinical concern	Items to check	Steps to remedy
hypoxia or hypoventilation	ABG, respiratory rate	intubate any patient who has hypercarbia, hypoxemia, or is not localizing
hypotension or hypertension	BP, Hgb/Hct	transfuse patients with significant loss of blood volume
anemia	Hgb/Hct	transfuse patients with significant anemia
seizures	electrolytes, AED levels	correct hyponatremia or hypoglycemia; administer AEDs when appropriate*
infection or hyperthermia	WBC, temperature	LP if meningitis is possible and no contraindications (*see page 201*)
spinal stability	spine x-rays	spine immobilization (spine board, cervical collar & sandbags…); patients with locked facets should be reduced if possible before transfer

* see Seizures, page 394, as well as Posttraumatic seizures on page 398

27.2. Management in E/R

27.2.1. Neurosurgical exam in trauma

The following describes some features that should be assessed under certain circumstances with the understanding that this must be individualized. This

addresses only craniospinal injuries.

General physical condition (oriented towards neuro assessment)

1. visual inspection of cranium:
   A. evidence of basal skull fracture (see *Basal skull fractures*, page 887):
      1. raccoon's eyes: periorbital ecchymoses
      2. Battle's sign: postauricular ecchymoses (around mastoid air sinuses)
      3. CSF rhinorrhea/otorrhea: *see page 301*
      4. hemotympanum or laceration of external auditory canal

   B. check for facial fractures
      1. LeFort fractures (*see page 890*): palpate for instability of facial bones, including zygomatic arch
      2. orbital rim fracture: palpable step-off

   C. periorbital edema, proptosis
2. cranio-cervical auscultation
   A. auscultate over carotid arteries: bruit may be associated with carotid dissection
   B. auscultate over globe of eye: bruit may indicate traumatic carotid-cavernous fistula (see *Carotid-cavernous fistula*, page 1113)
3. physical signs of trauma to spine: bruising, deformity
4. evidence of seizure: single, multiple, or continuing (status epilepticus)

Neurologic exam

1. cranial nerve exam
   A. optic nerve function
      1. if conscious: serial quantitation of vision in each eye is important[29] (*see page 863*). A Rosenbaum near vision card is ideal (*see inside back cover*), otherwise use any printed material. If patient cannot see this, check if they can count fingers. Failing this, check for hand motion vision and lastly light perception. Children may develop transient cortical blindness lasting 1-2 days, usually after a blow to the back of the head
      2. if unconscious: check for afferent pupillary defect (*see page 831*), best demonstrated with swinging flashlight test (*see page 830*).

Indicates possible optic nerve injury

3. funduscopic exam: check for papilledema, pre-retinal hemorrhages, retinal detachment, or retinal abnormalities suggestive of anterior optic nerve injury. If a detailed exam is required, pharmacologic dilatation with mydriatics may be employed, however, this precludes pupillary exam for a variable period of time, and should be undertaken advisedly (*see page 832*)

B. pupil: size in ambient light; reaction to light (direct & consensual)

C. VII: check for peripheral VII palsy (facial asymmetry of unilateral upper and lower facial muscles): see *Posttraumatic facial palsy*, page 889

D. VI: abducens palsy following trauma may occur as a result of ↑ ICP (*see page 836*) or with clival fractures (*see page 888*)

2. level of consciousness/mental status
   A. Glasgow coma scale for quantitating level of consciousness in poorly responsive patient (see *Table 12-1*, page 279)
   B. check orientation in patient able to communicate
3. motor exam (assesses motor tracts from motor cortex through spinal cord)
   A. if patient is cooperative: check motor strength in all 4 extremities
   B. if uncooperative: check for movement of all 4 extremities to noxious stimulus (differentiate voluntary movement from posturing or stereotypical spinal cord reflex). This also assesses sensation in an unresponsive patient
   C. if any doubt about integrity of spinal cord: also check "resting" tone of anal sphincter on rectal exam, evaluate voluntary sphincter contraction if patient can cooperate, check anal wink with pinprick, and assess bulbocavernosus reflex (see *Neurological assessment*, page 944 for details)
4. sensory exam
   A. cooperative patient:
      1. check pinprick on trunk and in all 4 extremities, touch on major dermatomes (C4, C6, C7, C8, T4, T6, T10, L2, L4, L5, S1, sacrococcygeal)
      2. check posterior column function: joint position sense of LEs
   B. uncooperative patient: check for central response to noxious stimulus (e.g. grimace, vocalization…, as opposed to flexion-withdrawal which could be a spinal cord mediated reflex)

5. reflexes
   A. muscle stretch ("deep tendon") reflexes if patient is not thrashing: e.g. preserved reflex indicates that a flaccid limb is due to CNS injury and not nerve root injury (and vice versa)
   B. check plantar reflex for upgoing toes (Babinski sign)
   C. in suspected spinal cord injury: the anal wink and bulbocavernosus reflex are checked on the rectal exam (*see above*)

INDICATIONS FOR CT AND ADMISSION CRITERIA FOR TBI

A multidisciplinary panel[30] prospectively followed 7,035 patients with head trauma to determine the probability of an intracranial injury **(ICI)** (and to evaluate the utility of skull x-rays **(SXR)** in head trauma, discussed only briefly here, *see page 859* for more). The panel stratified patients into one of three groups based on the likelihood of intracranial injury as outlined in the following sections. The breakdown is fairly similar to a 4 tier system based on an analysis of 10,000 patients in Italy[31].

CATEGORY 1. LOW RISK FOR INTRACRANIAL INJURY

Possible findings are shown in *Table 27-9*.

In this group, there is an extremely low likelihood of intracranial injury **(ICI)**, even if a skull fracture is present on SXR (incidence of ICI: $\leq$ 8.5 in 10,000 cases with 95% confidence level[30]). NB: this category excludes patients with a history of loss of consciousness.

Table 27-9 Findings with low risk of ICI

• asymptomatic
• H/A
• dizziness
• scalp hematoma, laceration, contusion, or abrasion
• no moderate nor high risk criteria (*see Table 27-11* and *Table 27-13*) (no loss of consciousness, etc.)

Management recommendations

CT scan is not usually indicated. Plain SXRs are not recommended: 99.6% of SXRs in this group are normal. Linear non-displaced skull fractures in this group require no treatment, although in-hospital observation (at least overnight) may be considered.

Patients in this group who meet *Criteria for observation at home* shown in *Table 27-12* (disregarding CT scan item) may be managed with observation at home with written head-injury discharge instructions, e.g as illustrated in *Table 27-10*.

Table 27-10 Sample discharge instructions for head injuries

Seek medical attention for any of the following: • a change in level of consciousness (including difficulty in awakening) • abnormal behavior • increased headache • slurred speech • weakness or loss of feeling in an arm or leg • persistent vomiting • enlargement of one or both pupils (the black round part in the middle of the eye) that does not get smaller when a bright light is shined on it • seizures (convulsions or fits) • significant increase in swelling at injury site
Do not take sedatives or pain medication stronger than Tylenol for 24 hours. Do not take aspirin or other anti-inflammatory medications.

CATEGORY 2. MODERATE RISK FOR INTRACRANIAL INJURY

Possible findings are shown in *Table 27-11*.

Table 27-11 Findings with moderate risk of ICI

• history of change or loss of consciousness on or after injury • progressive H/A • EtOH or drug intoxication • posttraumatic seizure • unreliable or inadequate history • age < 2 yr (unless trivial injury) • vomiting • posttraumatic amnesia • signs of basilar skull fracture • multiple trauma • serious facial injury • possible skull penetration or depressed fracture • suspected child abuse. • significant subgaleal swelling[31]

Table 27-12 Criteria for observation at home

1. normal cranial CT[32]
2. initial GCS ≥ 14
3. no high risk criteria (*see Table 27-13*)
4. no moderate risk criteria (*see Table 27-11*) except loss of consciousness
5. patient is now neurologically intact (amnesia for the event is acceptable)
6. there is a responsible, sober adult that can observe the patient
7. patient has reasonable access to return to the hospital E/R if needed
8. no "complicating" circumstances (e.g. no suspicion of domestic violence, including child abuse)

Management recommendations

1. brain CT scan (unenhanced): clinical grounds alone may miss important lesions in this group[32]. 8-46% of patients with minor head injury **(MHI)** have an intracranial lesion (the most frequent finding was hemorrhagic contusion)[33]
2. SXR: not recommended (*see page 859*) unless CT scan not available. Useless if normal. A SXR is helpful only if positive (a clinically unsuspected depressed skull fracture might be important)
3. observation
   A. at home, if the patient meets the criteria outlined in *Table 27-12*. Provide caregiver with written head-injury discharge instructions (sometimes called "subdural precautions"), as shown in *Table 27-10*
   B. in-hospital observation to rule-out neurologic deterioration if patient does not meet criteria in *Table 27-12* (including cases where CT scan is not done).

Managing patients with in-hospital observation and only getting a CT scan in cases of deterioration (GCS score ≤ 13) is as sensitive as CT in detecting intracranial hematomas[33-37], but is less cost effective than routinely performing an early CT scan and discharging patients who have a normal CT and no other indication for hospitalization[33]

CATEGORY 3. HIGH RISK FOR INTRACRANIAL INJURY

Possible findings are shown in *Table 27-13*.

Management recommendations

1. STAT unenhanced brain CT scan
2. admit
3. if there are focal findings, notify operating room to be on standby. For

rapid deterioration, consider emergency burr holes (see *Exploratory burr holes*, page 864)

4. determine if intracranial monitor is indicated (*see page 868*)
5. SXR usually not recommended: a fracture is rarely surprising, and a SXR is inadequate for assessing for intracranial injury. A SXR is possibly useful for localizing a radioopaque penetrating foreign body (knife blade, bullet…) for the O.R. (omit if significant delay required).

Table 27-13 Findings with high risk of ICI

• depressed level of consciousness not clearly due to EtOH, drugs, metabolic abnormalities, postictal, etc.
• focal neurological findings
• decreasing level of consciousness
• penetrating skull injury or depressed fracture

OTHER RISK FACTORS

Occipital vs. frontal fractures

Patients with occipital fractures may be at higher risk of significant intracranial injury **(ICI)**. May be related to the fact that in forward trauma, one may protect oneself with the outstretched arms. Furthermore, the facial bones and air sinuses exert an impact absorbing effect.

27.2.2. Radiographic evaluation

CT SCANS IN TRAUMA

An unenhanced (i.e. non-contrast) CT scan of the brain usually suffices for patients seen in the emergency department presenting after trauma or with a new neurologic deficit. Enhanced CT or MRI may be appropriate after the unenhanced CT, but are not usually required emergently (exceptions include: significant brain edema due to suspected neoplasm that is not demonstrated without contrast).

The main emergent conditions to rule out (and brief descriptions):

1. blood (hemorrhages or hematomas):
   A. extra-axial blood: surgical lesions are usually ≥ 1 cm maximal thickness
      1. epidural hematoma **(EDH)** (*see page 894*): usually biconvex and

often due to arterial bleeding

2. subdural hematoma **(SDH)** (*see page 896*): usually crescentic, usually due to venous bleeding. May cover larger surface area than EDH. Chronology of SDH: acute = high density, subacute ≈ isodense, chronic ≈ low density

B. subarachnoid blood (SAH): high density spread thinly over convexity and filling sulci or basal cisterns. Trauma is the most common cause of SAH. However, when the history of trauma is not clear, an arteriogram may be indicated to R/O a ruptured aneurysm (possibly precipitating the trauma)

C. intracerebral hemorrhage **(ICH)**: increased density in brain parenchyma

D. hemorrhagic contusion (*see page 893*): often "fluffy" inhomogeneous high-density areas within brain parenchyma adjacent to bony prominences (frontal and occipital poles, sphenoid wing). Less well defined than ICH

E. intraventricular hemorrhage: present in ≈ 10% of severe head injuries[38]. Associated with poor outcome; may be a marker for severe injury rather than the *cause* of the poor outcome. Use of intraventricular rt-PA has been reported for treatment[39] (*see page 1130*)

2. hydrocephalus: enlarged ventricles may sometimes develop following trauma
3. cerebral swelling: obliteration of basal cisterns (*see page 909*), compression of ventricles and sulci…
4. evidence of cerebral anoxia: loss of gray-white interface, signs of swelling
5. skull fractures:
   A. basal skull fractures (including temporal bone fracture)
   B. orbital blow-out fracture
   C. calvarial fracture (CT may miss some linear nondisplaced skull fractures)
      1. linear vs. stellate
      2. open vs. closed
      3. diastatic (separation of sutures)
      4. depressed vs. nondepressed: CT helps assess need for surgery
6. ischemic infarction: findings are usually minimal or subtle if < 24 hrs since CVA

7. pneumocephalus: may indicate skull fracture (basal or open convexity)
8. shift of midline structures (due to extra- or intra-axial hematomas or asymmetric cerebral edema): shift can cause altered levels of consciousness (*see page 280*)

Indications for initial brain CT

1. presence of any moderate[40] or high risk criteria (*see Table 27-11* and *Table 27-13*) which include: GCS ≤ 14, unresponsiveness, focal deficit, amnesia for injury, altered mental status (including those that are significantly inebriated), deteriorating neuro status, signs of basal or calvarial skull fracture
2. assessment prior to general anesthesia for other procedures (during which neurologic exam cannot be followed in order to detect delayed deterioration)

Follow-up CT

Routine follow-up CT (when there is no indication for *urgent* follow-up CT, *see below*):

1. for patients with severe head injuries:
   A. for stable patients, follow-up CTs are usually obtained between day 3 to 5, (some recommend at 24 hrs also) and again between day 10 to 14
   B. some recommend routine follow-up CT several hours after the "time zero" CT (i.e. initial CT done within hours of the trauma) to rule-out delayed EDH (*see page 896*), SDH (*see page 899*), or traumatic contusions[41] (*see page 893*)
2. for patients with mild to moderate head injuries:
   A. with an abnormal initial CT, the CT scan is repeated prior to discharge
   B. stable patients with mild head injury and normal initial CT do not require follow-up CT

Urgent follow-up CT: performed for neurological deterioration (loss of 2 or more points on the GCS, development of hemiparesis or new pupillary asymmetry), persistent vomiting, worsening H/A, seizures or unexplained rise in intracranial pressure **(ICP)**.

SPINE FILMS

1. cervical spine: must be cleared radiographically from the cranio-cervical

junction down through and including the C7-T1 junction. Spinal injury precautions (cervical collar…) are continued until the C-spine is cleared. The steps in obtaining adequate films are outlined in *Spine injuries*, *Radiographic evaluation and initial C-spine immobilization* on page 938

2. thoracic and lumbosacral spine films should be obtained based on physical findings and on mechanism of injury (see *Spine injuries*, *Radiographic evaluation and initial C-spine immobilization* on page 938)

SKULL X-RAYS

A skull fracture increases the probability of a surgical intracranial injury **(ICI)** (in a comatose patient it is a 20-fold increase, in a conscious patient it is a 400-fold increase[42, 43]). However, significant ICI can occur with a normal SXR (SXR was normal in 75% of minor head injury patients found to have intracranial lesions on CT, attesting to the insensitivity of SXRs[33]). SXRs affect management of only 0.4-2% of patients in most reports[30].

A SXR may be helpful in the following:

1. in patients with moderate risk for intracranial injury (see *Table 27-11*, page 857) by detecting an unsuspected depressed skull fracture (however, most of these patients will get a CT scan, which obviates the need for SXR)
2. if a CT scan cannot be obtained, a SXR may identify significant findings such as pineal shift, pneumocephalus, air-fluid levels in the air sinuses, skull fracture (depressed or linear)… (however, sensitivity for detecting ICI is very low)
3. with penetrating injuries: helps in visualization of some metallic objects

MRI SCANS IN TRAUMA

Usually not appropriate for acute head injures. While MRI is more sensitive than CT, there were no surgical lesions demonstrated on MRI that were not evident on CT 44.

MRI may be helpful later after the patient is stabilized, e.g. to evaluate brainstem injuries, small white matter changes[45] (e.g. punctate hemorrhages in the corpus callosum seen in diffuse axonal injury, *see page 853*)… Spinal MRI is indicated in patients with spinal cord injuries.

ARTERIOGRAM IN TRAUMA

Cerebral arteriogram: useful with non missile penetrating trauma (*see page 916*).

27.2.3. E/R management specifics

INITIAL RESUSCITATION

PRACTICE GUIDELINE 27-2 IBP AND OXYGENATION
Level II[46]: monitor BP and avoid hypotension (SBP < 90 mm Hg) **Level III**[46]: monitor oxygenation and avoid hypoxia (PaO_2 < 60 mm Hg or O_2 saturation < 90%)

ADMITTING ORDERS FOR MINOR OR MODERATE HEAD INJURY

Admitting orders for <u>minor</u> head injury (GCS≥ 14[A])[B]

1. activity: BR with HOB elevated 30-45°
2. neuro checks q 2 hrs (q 1 hr if more concerned; consider ICU for these patients). Contact physician for neurologic deterioration
3. NPO until alert; then clear liquids, advance as tolerated
4. isotonic IVF (e.g. NS + 20 mEq KCl/L) run at maintenance: ≈ 100 cc/hr for average size adult (peds: 2000 $cc/m^2/d$)[C]
5. mild analgesics: acetaminophen (PO, or PR if NPO), codeine if necessary
6. anti-emetic: give infrequently to avoid excessive sedation, avoid phenothiazine anti-emetics (which lower the seizure threshold); e.g. use trimethobenzamide (Tigan®) 200 mg IM q 8 hrs PRN for adults

Admitting orders for <u>moderate</u> head injury (GCS 9-13)[B]

1. orders as for minor head injury (*see above*) except patient is kept NPO in case surgical intervention is needed (including ICP monitor)
2. for GCS = 9-12 admit to ICU. For GCS = 13, admit to ICU if CT shows any significant abnormality (hemorrhagic contusions unless very small, rim subdural…)
3. patients with normal or near-normal CTs should improve within hours. Any patient who fails to reach a GCS of 14-15 within 12 hrs should have a repeat CT at that time[40]

Early use of paralytics and sedation (prior to ICP monitoring)

PRACTICE GUIDELINE 27-3 Early sedation and paralysis
Level III[47]: sedation and neuromuscular blockade (NMB) can be helpful for transporting the head-injured patient, but they interfere with the neuro exam **Level III**[47]: NMB should be used when sedation alone is inadequate

The routine use of sedatives and paralytics in neurotrauma patients may lead to a higher incidence of pneumonia, longer ICU stays, and possibly sepsis[48]. These agents also impair neurologic assessment[47, 49]. Use should therefore be reserved for cases with clinical evidence of intracranial hypertension (*see Table 27-14*), or where use is necessary for transport or to permit evaluation of the patient[50].

A. traditionally, mild head injury has been defined as GCS ≥ 13. However, the increased frequency of both surgical lesions and CT scan abnormalities in patients with GCS = 13 suggests that they would be better classified with the *moderate* rather than mild head injuries[32]

B. see *Indications for CT and admission criteria for TBI* on page 856 for admitting criteria

C. the concept of "running the patient dry" is considered obsolete (*see page 878*)

Table 27-14 Clinical signs of IC-HTN*

1. pupillary dilatation (unilateral or bilateral)
2. asymmetric pupillary reaction to light
3. decerebrate or decorticate posturing (usually contralateral to blown† pupil)
4. progressive deterioration of the neurologic exam not attributable to extracranial factors

* Items 1-3 represent clinical signs of herniation. The most convincing clinical evidence of IC-HTN is the witnessed evolution of 1 or more of these signs. IC-HTN may produce a bulging fontanelle in an infant.

† "blown pupil": fixed & dilated pupil

Intubation and hyperventilation

Indications for intubation in trauma (also *see PRACTICE GUIDELINE 27-4*):

1. depressed level of consciousness (patient cannot protect airway): usually GCS ≤ 7
2. need for hyperventilation **(HPV)**: *see below*

3. severe maxillofacial trauma: patency of airway tenuous
4. need for pharmacologic paralysis for evaluation or management

PRACTICE GUIDELINE 27-4 INTUBATION - INDICATIONS

Level III[51]: secure the airway (usually by endotracheal intubation) in patients with GCS ≤ 8 who are unable to maintain their airway or who remain hypoxic despite supplemental O_2

Cautions regarding intubation:

1. if basal skull fracture through cribriform plate is possible, avoid nasotracheal intubation (to avoid intracranial entry of tube). Use orotracheal intubation
2. prevents assessment of patient's ability to verbalize[49] e.g. for determining Glasgow Coma Scale score
3. risk of pneumonia: *see PRACTICE GUIDELINE 27-5* regarding antibiotics

PRACTICE GUIDELINE 27-5 ANTIBIOTICS FOR INTUBATION

Level II[52]: periprocedural antibiotics for endotracheal intubation reduce the risk of pneumonia, but do not alter length of stay or mortality

Hyperventilation (HPV)

PRACTICE GUIDELINE 27-6 EARLY/PROPHYLACTIC HYPERVENTILATION

Level II[53]: prophylactic hyperventilation ($PaCO_2 \leq 25$ mm Hg) is not recommended

Level III

- hyperventilation **(HPV)** before ICP monitoring is established should be reserved as a temporizing measure[53] for patients with signs of transtentorial herniation (*see Table 27-14*) or progressive neurologic deterioration not attributable to extracranial causes[47]
- HPV should be avoided during the first 24 hrs after TBI (when CBF is often dangerously decreased)[53]

1. since HPV may exacerbate cerebral ischemia, HPV should not be used prophylactically (*see* *page 880*)
2. prior to ICP monitoring, HPV should only be used briefly when CT or clinical signs of IC-HTN are present[50] (*see* *Table 27-14* for clinical signs)
   A. when appropriate indications are met: HPV to $PaCO_2$ = 30-35 mm Hg
   B. HPV should not be used to the point that $PaCO_2$ < 30 mm Hg (this further reduces CBF but does not necessarily reduce ICP)
3. acute alkalosis increases protein binding of calcium (decreases ionized Ca^{++}). Patients being hyperventilated may develop ionized hypocalcemia with tetany (despite normal total [Ca])

MANNITOL IN THE E/R

PRACTICE GUIDELINE 27-7 EARLY USE OF MANNITOL

Level III[47, 54]: the use of mannitol before ICP monitoring is established should be reserved for patients who are adequately volume-resuscitated with signs of transtentorial herniation (*see* *Table 27-14*) or progressive neurologic deterioration not attributable to extracranial causes

Indications in E/R (also *see* *page 882* for more details):
1. evidence of intracranial hypertension (*see* *Table 27-14*)
2. evidence of mass effect (focal deficit, e.g. hemiparesis)
3. sudden deterioration prior to CT (including pupillary dilatation)
4. after CT, if a lesion that is associated with increased ICP is identified
5. after CT, if going to O.R.
6. to assess “salvageability”: in patient with no evidence of brainstem function, look for return of brainstem reflexes

Contraindications:
1. prophylactic administration is not recommended due to its volume-depleting effect. Use only for appropriate indications (*see above*)
2. hypotension or hypovolemia: hypotension can negatively influence outcome[50]. Therefore, when intracranial hypertension **(IC-HTN)** is present, first utilize sedation and/or paralysis, and CSF drainage. If further measures are needed, fluid resuscitate the patient before administering

mannitol. Use hyperventilation in hypovolemic patients until mannitol can be given

3. relative contraindication: mannitol may slightly impede normal coagulation
4. CHF: before causing diuresis, mannitol transiently increases intravascular volume. Use with caution in CHF, may need to pre-treat with furosemide (Lasix®)

Rx: bolus with 0.25-1 gm/kg over < 20 min (for average adult: ≈ 350 ml of 20% solution). Peak effect occurs in ≈ 20 minutes (*see page 882* for follow-up dosing).

PROPHYLACTIC ANTIEPILEPTIC DRUGS (AEDS)

PRACTICE GUIDELINE 27-8 PROPHYLACTIC ANTICONVULSANTS AFTER TBI

Level II[55-57]: prophylactic phenytoin, carbamazepine, phenobarbital or valproate[58] do not prevent *late* PTS
Level II: AEDs[57] (e.g. phenytoin, valproate, or carbamazepine[55, 56, 58]) may be used to decrease the incidence of *early* PTS (within 7 days of TBI) in patients at high risk of seizures after TBI (*see Table 27-15*), however, this does not improve outcome

Routine use of prophylactic antiepileptic drugs **(AEDs)** in traumatic brain injury **(TBI)** is ineffective in preventing the late development of posttraumatic seizures **(PTS)** i.e. epilepsy, and has been shown to not be useful except in certain circumstances[55, 56].

See page 399 for details on using and discontinuing prophylactic AEDs following TBI. (*Table 27-15* reiterates the markers for patients at increased risk of early PTSs).

Table 27-15 Conditions with increased risk of posttraumatic seizures

1. acute subdural, epidural, or intracerebral hematoma
2. open-depressed skull fracture with parenchymal injury
3. seizure within the first 24 hrs after injury
4. Glasgow Coma Scale score < 10
5. penetrating brain injury
6. history of significant alcohol abuse
7. ± cortical (hemorrhagic) contusion on CT

POSTTRAUMATIC SUBARACHNOID HEMORRHAGE

AKA traumatic SAH **(tSAH)**. Trauma is the most common cause of SAH. There is some evidence that nimodipine (Nimotop®) may improve outcome in head-injured patients with subarachnoid blood detected on CT[59]. ***Rx***: 60 mg PO or per NG q 4 hrs, hold for hypotension (*see page 1053*). For hydrocephalus after tSAH, *see page 906*.

PATIENTS WITH ASSOCIATED SEVERE SYSTEMIC INJURIES

Hypotension (defined as a single SBP < 90 mm Hg) doubles mortality, hypoxia (apnea or cyanosis, or PaO_2 < 60 mm Hg on ABG) also increases mortality[60], and the combination of both triples mortality and increases the risk bad outcome.

In centers where diagnostic peritoneal lavage **(DPL)** is used to assess for intraabdominal hemorrhage, if the initial fluid is not grossly bloody and the patient is hemodynamically stable, the patient should be taken for cranial CT while the remainder of the lavage fluid is collecting for quantitative analysis.

Patients with grossly positive DPL and/or hemodynamic instability may need to be rushed to the O.R. for emergent laparotomy by trauma surgeons without benefit of cerebral CT. These guidelines are offered:

✖ CAUTION: many patients with severe trauma may be in DIC (either due to systemic injuries, or directly related to severe head injury possibly because the brain is rich in thromboplastin[61]). Operating on patients in DIC is usually disastrous. At the least, check the PT/PTT

1. if neuro-exam is relatively good (i.e. GCS > 8, which implies at least localizing)
   A. operative neurosurgical intervention is probably not required
   B. utilize good neuroanesthesia techniques (elevate head of bed, judicious administration of IV fluids, avoiding prophylactic hyperventilation…)
   C. obtain a head CT scan immediately post-op
2. if patient has focal neurologic deficit, an exploratory burr-hole should be placed in the O.R. simultaneously with the treatment of other injuries. Placement is guided by the pre-op deficit (see *Exploratory burr holes*, page 864)
3. if there is severe head injury (GCS ≤ 8) without localizing signs, or if initial burr hole is negative, or if there is no pre-op neuro exam, then

A. measure the ICP: insert a ventriculostomy catheter (if the lateral ventricle cannot be entered after 3 passes, an intraparenchymal fiber-optic monitor or subarachnoid bolt should be used)
   1. normal ICP: unlikely that a surgical lesion exists. Manage ICP medically and, if a IVC was inserted, with CSF drainage
   2. elevated ICP (≥ 20 mm Hg): inject 3-4 cc of air into ventricles through IVC, then obtain portable intraoperative AP skull x-ray (intraoperative pneumoencephalogram) to determine if there is any midline shift
      a. mass effect with ≥ 5 mm of midline shift is explored[62] with burr-hole(s) on the side opposite the direction of shift
      b. if no mass effect, intracranial hypertension is managed medically and with CSF drainage

B. routine use of exploratory burr holes for children with GCS = 3 has been found not to be justified[63]

INDIRECT OPTIC NERVE INJURY

≈ 5% of head trauma patients manifest an associated injury to some portion of the visual system. Approximately 0.5-1.5% of head trauma patients will sustain *indirect* injury (as opposed to penetrating trauma) to the optic nerve, most often from an ipsilateral blow to the head (usually frontal, occasionally temporal, rarely occipital)[29]. The optic nerve may be divided into 4 segments: intraocular (1 mm in length), intraorbital (25-30 mm), intracanalicular (10 mm), and intracranial (10 mm). The intracanalicular segment is the most common one damaged with closed head injuries. Funduscopic abnormalities visible on initial exam indicates anterior injuries (injury to the intraocular segment (optic disc) or the 10-15 mm of the intraorbital segment immediately behind the globe where the central retinal artery is contained within the optic nerve), whereas posterior injuries (occurring posterior to this but anterior to the chiasm) takes 4-8 weeks to show signs of disc pallor and loss of the retinal nerve fiber layer.

Treatment[29]: No prospective study has been carried out. Optic nerve decompression has been advocated for indirect optic nerve injury, however, the results are not clearly better than expectant management with the exception that documented delayed visual loss appears to be a strong indication for surgery. Transethmoidal is the accepted route, and is usually done within 1-3 weeks from the trauma[64]. The use of “megadose steroids” may be appropriate as an adjunct to diagnosis and treatment.

POST-TRAUMATIC HYPOPITUITARISM

Trauma is a rare cause of hypopituitarism. It may follow closed head injury (with or without basilar skull fracture) or penetrating trauma[65]. In 20 cases in the literature[66] all had deficient growth hormone and gonadotropin, 95% had corticotropin deficiency, 85% had reduced TSH, 63% had elevated PRL. Only 40% had transient or permanent DI.

27.2.4. Exploratory burr holes

In a trauma patient, the clinical triad of altered mental status, unilateral pupillary dilatation with loss of light reflex, and contralateral hemiparesis is most often due to upper brainstem compression by uncal transtentorial herniation which, in the majority of trauma cases, is due to an extraaxial intracranial hematoma. Furthermore, the prognosis of patients with traumatic herniation is poor. Outcome may possibly be improved slightly by increasing the rapidity with which decompression is undertaken, however, an upper limit of salvageability is probably still only ≈ 20% satisfactory outcome.

Burr holes are primarily a <u>diagnostic tool</u>, as bleeding cannot be controlled and most acute hematomas are too congealed to be removed through a burr hole. However, if the burr hole is positive, it is possible that modest decompression may be performed, and then the definitive craniotomy can be undertaken incorporating the burr hole(s).

With widespread availability of quickly accessible CT scanning, exploratory burr holes are infrequently indicated.

INDICATIONS

1. clinical criteria: based on deteriorating neurologic exam. Indications in E/R (rare): patient dying of rapid transtentorial herniation (*see below*) or brainstem compression that does not improve or stabilize with mannitol and hyperventilation[67].
   - indicators of transtentorial herniation/brainstem compression:
     1. sudden drop in Glasgow Coma Scale **(GCS)** score
     2. one pupil fixes and dilates
     3. paralysis or decerebration (usually contralateral to blown pupil)
   - recommended situations where criteria should be applied:
     1. neurologically stable patient undergoes <u>witnessed</u> deterioration as described above

        2. awake patient undergoes same process in transport, and changes are well documented by competent medical or paramedical personnel
2. other criteria
   A. some patients needing emergent surgery for systemic injuries (e.g. positive peritoneal lavage + hemodynamic instability) where there is not time for a brain CT (see *Patients with associated severe systemic injuries*, page 863)

MANAGEMENT

Controversial. The following should serve only as guidelines:

1. if patient fits the above criteria (emergent operation for systemic injuries or deterioration with failure to improve with mannitol and hyperventilation), and CT scan cannot be performed and interpreted immediately, then treatment should not wait for CT scan
   A. in general, if the O.R. can be immediately available, burr holes are preferably done there (equipped to handle craniotomy, better lighting and sterility, dedicated scrub nurse…) especially in older patients (> 30 yrs) not involved in MVAs (see *Literature* below). This may more rapidly diagnose and treat extraaxial hematomas in herniating patients, although no difference in outcome has been proven
   B. if delay in getting to the O.R. is foreseen, emergency burr holes in the E/R should be performed
2. placement of burr-hole(s) as outlined under *Technique* below)

TECHNIQUE

Position

Shoulder roll, head turned with side to be explored up. Three pin skull-fixation used if concern about possible aneurysm or AVM (to allow for retractors and increased stability) or if additional stability is desired (e.g. with unstable cervical fractures), otherwise a horse-shoe head-holder suffices and saves time and permits rapid access to the other side.

Choice of side for initial burr hole

Start with a temporal burr hole (*see below*) on the side:

1. ipsilateral to a blown pupil. This will be on the correct side in > 85% of epidurals[68] and other extra-axial mass lesions[69]
2. if both pupils are dilated, use the side of the first dilating pupil (if known)
3. if pupils are equal, or it is not known which side dilated first, place on side of obvious external trauma
4. if no localizing clues, place hole on left side (to evaluate and decompress the dominant hemisphere)

Approach

Burr holes are placed along a path that can be connected to form a "trauma flap" if a craniotomy becomes necessary (*see Figure 27-1*). The "trauma flap" is so-called because it provides wide access to most of the cerebral convexity permitting complete evacuation of acute blood clot and control of most bleeding.

First outline the trauma flap with a skin marker:

1. start at the zygomatic arch < 1 cm anterior to the tragus (spares the branch of the facial nerve to the frontalis muscle and the anterior branch of the superficial temporal artery)
2. proceed superiorly and then curve posteriorly at the level of top of the pinna
3. 4-6 cm behind the pinna it is taken superiorly
4. 1-2 cm ipsilateral to the midline (sagittal suture) curve anteriorly to end behind the hairline

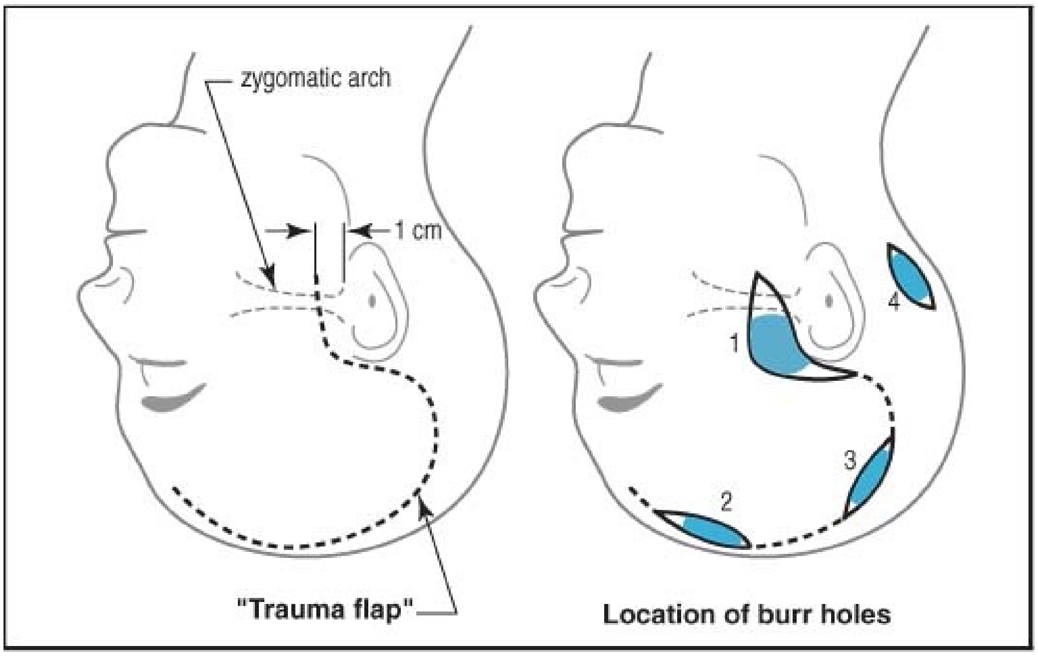


Figure 27-1 Technique to convert burr-hole(s) into trauma flap (adapted[69, 70])

Burr hole locations

1. first (temporal) burr-hole: over middle cranial fossa (#1 in *Figure 27-1*) just superior to the zygomatic arch. Provides access to middle fossa (the most common site of epidural hematoma) and usually allows access to most convexity subdural hematomas, as well as proximity to middle meningeal artery in region of pterion
2. if no epidural hematoma, the dura is opened if it has bluish discoloration (suggests subdural hematoma) or if there is a strong suspicion of a mass lesion on that side
3. if completely negative, usually perform temporal burr hole on contralateral side
4. if negative, further burr holes should be undertaken if a CT cannot now be done
5. proceed to ipsilateral frontal burr hole (#2 in *Figure 27-1*)
6. subsequent burr holes may be placed at parietal region (#3 in *Figure 27-1*) and lastly in posterior fossa (#4 in *Figure 27-1*)

LITERATURE

In 100 trauma patients undergoing transtentorial herniation or brainstem compression[69], exploratory burr holes (bilateral temporal, frontal and parietal,

done in the O.R.) were positive in 56%. Lower rates in younger patients (< 30 yrs) and those in MVAs (as opposed to falls or assaults). SDH was the most common extraaxial mass lesion (alone and unilateral in 70%, bilateral in 11%, and in combination with EDH or ICH in > 9%).

When burr holes were positive, the first burr hole was on the correct side 86% of the time when placed as above. Six patients had significant extraaxial hematomas missed with exploratory burr holes (mostly due to incomplete burr hole exploration). Only 3 patients had the above neurologic findings as a result of intraparenchymal hematomas.

Outcome

Mean follow-up: 11 mos (range: 1-37). 70 of the 100 patients died. No morbidity or mortality was directly attributable to the burr holes. Four patients with good outcome and 4 with moderate disability had positive burr holes.

27.3. Neuromonitoring

This section considers neuromonitoring instrumentation that can be done primarily at the patient's bedside. The bulk of neuromonitoring literature deals with intracranial pressure (ICP). Other parameters that can be monitored include: jugular venous oxygen monitoring (*page 874*), regional CBF (*page 875*), brain tissue oxygen tension (*page 874*), and brain metabolites (pyruvate, lactate, glucose…) (*page 875*).

The role of adjunctive monitoring is currently unknown. Unanswered questions include: should neuromonitoring be disease specific (e.g. is SAH different from TBI), which monitors provide additional unique information, what are the critical values of the monitored entity, and what interventions should be undertaken to correct abnormalities?

27.3.1. Intracranial pressure (ICP)

Intracranial pressure **(ICP)** is discussed in this section on trauma because of the close relationship between elevated ICP and brain damage from head injury. However, factors involved in diagnosing and treating intracranial hypertension **(IC-HTN)** also may pertain (with modifications) to brain tumors, dural venous thrombosis, etc.

27.3.1.1. General information about ICP

CEREBRAL PERFUSION PRESSURE (CPP) AND CEREBRAL AUTOREGULATION

Secondary brain injury (i.e. following the initial trauma) is attributable in part to cerebral ischemia (see *Secondary injury*, page 854). The critical parameter for brain function and survival is not actually ICP, rather it is adequate cerebral blood flow **(CBF)** to meet $CMRO_2$ demands (for a discussion of CBF & $CMRO_2$, *see page 1010*). CBF is difficult to quantitate, and can only be measured continuously at the bedside with specialized equipment and difficulty[71]. However, CBF depends on cerebral perfusion pressure **(CPP)**, which is related to ICP (which is more easily measured) as shown in *Eq 27-1*.

$$\begin{Bmatrix}\text{cerebral perfusion}\\ \text{pressure}\end{Bmatrix} = \begin{Bmatrix}\text{mean arterial}\\ \text{pressure*}\end{Bmatrix} - \begin{Bmatrix}\text{intracranial}\\ \text{pressure}\end{Bmatrix} \qquad \textbf{Eq 27-1}$$

or, expressed in symbols:

$$CPP = MAP^* - ICP$$

* note: the actual pressure of interest is the **mean carotid pressure (MCP)** which may be approximated as the MAP with the transducer zeroed ≈ at the level of the foramen of Monro[72]

Normal adult CPP is > 50 mm Hg. **Cerebral autoregulation** is a mechanism whereby over a wide range, large changes in systemic BP produce only small changes in CBF. Due to autoregulation, CPP would have to drop below 40 in a normal brain before CBF would be impaired.

In the head injured patient, recent evidence suggests that elevated ICP (≥ 20 mm Hg) may be more detrimental than changes in CPP (as long as CPP is > 60 mm Hg[73])[18] (higher levels of CPP were not protective against significant ICP elevations[18]).

INTRACRANIAL PRESSURE

The following are approximations to help simplify understanding ICP (these are only models, and as such are not entirely accurate):

1. normal intracranial constituents (and approximate volumes):
   A. brain parenchyma (which also contains extracellular fluid): 1400 ml
   B. cerebral blood volume **(CBV)**: 150 ml
   C. cerebrospinal fluid **(CSF)**: 150 ml
2. these volumes are contained in an inelastic, completely closed skull
3. pressure is distributed evenly throughout the intracranial cavity

4. the modified **Monro-Kellie** doctrine[74] states that the sum of the intracranial volumes (CBV, brain, CSF, and other constituents (e.g. tumor, hematoma…)) is constant, and that an increase in any one of these must be offset by an equal decrease in another
   - the mechanism: there is a pressure equilibrium in the skull. If the pressure from one intracranial constituent increases (as when that component increases in volume), it causes the pressure inside the skull (ICP) to increase. When this increased ICP exceeds the pressure required to force one of the other constituents out through the foramen magnum **(FM)** (the only true effective opening in the intact skull) that other component will decrease in size via that route until a new equilibrium is established. The craniospinal axis can buffer small increases in volume with no change or only a slight increase in ICP. If the expansion continues, then the new equilibrium will be at a higher ICP. The result:
   - at pressures slightly above normal, if there is no obstruction to CSF flow (obstructive hydrocephalus), CSF can be displaced from the ventricles and subarachnoid spaces and exit the intracranial compartment via the FM
   - intravenous blood can also be displaced through the FM via the IJVs
   - as pressure continues to rise, arterial blood is displaced and CPP decreases, eventually producing diffuse cerebral ischemia. At pressures equal to mean arterial pressure, arterial blood will be unable to enter the skull through the FM, producing complete cessation of blood flow to the brain, with resultant massive infarction
   - increased brain edema, or an expanding mass (e.g. hematoma) can push brain parenchyma downward into the foramen magnum (cerebral herniation) although brain tissue cannot actually exit the skull

Normal ICP

The normal range of ICP varies with age. Values for pediatrics are not well established. Guidelines are shown in *Table 27-16*.

Intracranial hypertension (IC-HTN)

Traumatic IC-HTN may be due any of the following (alone or in various combinations):

1. cerebral edema
2. hyperemia: the normal response to head injury[76]. Possibly due to

vasomotor paralysis (loss of cerebral autoregulation). May be more significant than edema in raising ICP[17] (*see page 902*)

3. traumatically induced masses
   A. epidural hematoma
   B. subdural hematoma
   C. intraparenchymal hemorrhage (hemorrhagic contusion)
   D. foreign body (e.g. bullet)
   E. depressed skull fracture
4. hydrocephalus due to obstruction of CSF absorption or circulation
5. hypoventilation (causing hypercarbia → vasodilatation)
6. systemic hypertension (HTN)
7. venous sinus thrombosis
8. increased muscle tone and valsalva maneuver as a result of agitation or posturing → increased intrathoracic pressure → increased jugular venous pressure → reduced venous outflow from head
9. sustained posttraumatic seizures (status epilepticus)

Table 27-16 Normal ICP

Age group	Normal range (mm Hg)
adults and older children*	< 10-15
young children	3-7
term infants†	1.5-6

* the age of transition from “young” to “older” child is not precisely defined

† may be subatmospheric in newborns[75]

A <u>secondary increase in ICP</u> is sometimes observed 3-10 days following the trauma, and may be associated with a worse prognosis[77]. Possible causes include:

1. delayed hematoma formation
   A. delayed epidural hematoma: *see page 896*
   B. delayed acute subdural hematoma: *see page 899*
   C. delayed traumatic intracerebral hemorrhage[41] (or hemorrhagic contusions) with perilesional edema: usually in older patients, may cause sudden deterioration. May be severe enough to require evacuation (*see page 893*)
2. cerebral vasospasm[78]

3. severe adult respiratory distress syndrome **(ARDS)** with hypoventilation
4. delayed edema formation: more common in pediatric patients
5. hyponatremia

Indications to treat IC-HTN

Various cutoff values are used at different centers above which treatment measures for intracranial hypertension **(IC-HTN)** are initiated. Although 15, 20 and 25 have been quoted, most centers use **ICP ≥ 20-25 mm Hg** as the upper limit[50]. There is high mortality and worse outcome[18] among patients with ICP persistently > 20 compared to 20% in those where ICP could be kept < 2079. Better control may be possible by treating early rather than waiting and trying to control higher ICPs or when plateau waves occur[27].

"Deadly" ICP (in adult), i.e. likely to be fatal if uncontrolled: > 25-30 mm Hg.

Cushing's triad

Cushing's triad is shown in *Table 27-17*, and may be seen with IC-HTN regardless of cause. However, the full triad is only seen in ≈ 33% of cases of IC-HTN.

Table 27-17 Cushing's triad

A. hypertension
B. bradycardia
C. respiratory irregularity

CT scan and elevated ICP

Whereas CT findings may be correlated with a *risk* of IC-HTN, no combination of CT findings has been shown to allow accurate estimates of actual ICP. 60% of patients with closed head injury and an abnormal CT[A] will have IC-HTN[80].

A. "abnormal" CT: demonstrates hematomas (EDH, SDH or ICH), contusions[80], compression of basal cisterns (*see page 909*), herniation or swelling[81, 82]

Only 13% of patients with a normal CT scan will have IC-HTN[80]. However, patients with a normal CT *AND* 2 or more risk factors identified in *Table 27-18* will have ≈ 60% risk of IC-HTN. If only 1 or none are present, ICP will be increased in only 4%.

Table 27-18 Risk factors for ICHTN with a normal CT

• age > 40 yrs
• SBP < 90 mm Hg
• decerebrate or decorticate posturing on motor exam (unilateral or bilateral)

27.3.1.2. ICP monitoring

INDICATIONS FOR ICP MONITORING

PRACTICE GUIDELINE 27-9 INDICATIONS FOR ICP MONITORING

For salvageable patients with severe traumatic brain injury (GCS ≤ 8 after cardiopulmonary resuscitation)
Level II[82]: with an abnormal admitting brain CTA
Level III[82]: with a normal admitting brain CT, but with ≥ 2 of the risk factors for IC-HTN in *Table 27-18*

★ 1. neurologic criteria: *see PRACTICE GUIDELINE 27-9* above
   - some centers monitor patients who don't follow commands. Rationale: patients who follow commands (GCS ≥ 9) are at low risk for IC-HTN, and one can follow sequential neurologic exams in these patients and institute further evaluation or treatment based on neurologic deterioration
   - some monitor patients who don't localize, and follow neuro exam on others

2. multiple systems injured with altered level of consciousness (especially where therapies for other injuries may have deleterious effects on ICP, e.g. high levels of PEEP or the need for large volumes of IV fluids or the need for heavy sedation)
3. with traumatic intracranial mass (EDH, SDH, depressed skull fracture…)
   A. a physician may choose to monitor ICP in some of these patients[81, 83]
   B. post-op, subsequent to removal of the mass

4. non-traumatic indications for ICP monitoring:
   A. some centers monitor ICP in patients with acute fulminant liver failure with an INR > 1.5 and Grade III of IV coma. A recent study shows that a subarachnoid bolt may be inserted after administration of factor VII 40 mcg/kg IV over 1-2 minutes (the bolt is inserted as soon as possible (usually within 15 minutes and no more than 2 hours after administration)) without significant risk of hemorrhage. All patients were treated with hypothermia; other ICP treatment measures were used for refractory IC-HTN

CONTRAINDICATIONS (RELATIVE)

1. "awake" patient: monitor usually not necessary, can follow neuro exam
2. coagulopathy (including DIC): frequently seen in severe head injury. If an ICP monitor is essential, take steps to correct coagulopathy (FFP, platelets…) and consider subarachnoid bolt or epidural monitor (an IVC or intraparenchymal monitor is contraindicated) (for recommended range of PT or INR, *see page 37*)

DURATION OF MONITORING

D/C monitor when ICP normal **x** 48-72 hrs after withdrawal of ICP therapy. Caution: IC-HTN may have delayed onset (often starts on day 2-3, and day 9-11 is a common second peak especially in peds). Also see *Delayed deterioration*, page 854. Avoid a false sense of security imparted by a normal early ICP.

COMPLICATIONS OF ICP MONITORS

See *Table 27-19* for a summary of complication rates for various types of monitors[50].

1. infection: *see below*
2. hemorrhage[50]: overall incidence is 1.4% for all devices (*see Table 27-19* for breakdown). Risk of significant hematoma requiring surgical evacuation is ≈ 0.5–2.5%[80, 86, 87]
3. malfunction or obstruction: with fluid coupled devices, higher rates of obstruction occur at ICPs > 50 mm Hg
4. malposition: 3% of IVCs require operative repositioning

Table 27-19 Complication rates with various types of ICP monitors

Monitor type	Bacterial colonization*	Hemorrhage	Malfunction or obstruction
IVC	ave: 10-17% range[84, 85]: 0-40%	1.1%	6.3%
subarachnoid bolt	ave: 5% range: 0-10%	0	16%
subdural	ave: 4% range: 1-10%	0	10.5%
parenchymal	ave: 14% (two reports, 12% & 17%)	2.8%	9-40%

* some studies report this as infection, but do not distinguish between clinically significant infection and colonization of ICP monitor

Infection with ICP monitors

Colonization of the monitoring device is much more common than clinically significant infection (ventriculitis or meningitis). See *Table 27-19* for colonization rates. Fever, leukocytosis and CSF pleocytosis have low predictive value (CSF cultures are more helpful). Range of reported infection rates: 1-27%[88].

PRACTICE GUIDELINE 27-10 INFECTION PROPHYLAXIS WITH ICP MONITORS

Level III[52]: neither prophylactic antibiotics nor routine ventricular catheter exchange is recommended to reduce infection

Identified risk factors for infection include[85, 88-90]:

1. intracerebral, subarachnoid or intraventricular hemorrhage
2. ICP > 20 mm Hg
3. duration of monitoring: contradictory results in literature. One study found an increased risk with monitor duration > 5 days (infection risk reaches 42% by day #11)[86, 89]. Another found no correlation with monitoring duration[91]. A analysis[85] found a non-linear increase of risk during the first 10-12 days after which the rate diminished rapidly
4. neurosurgical operation: including operations for depressed skull fracture
5. irrigation of system
6. leakage around IVCs

7. open skull fractures (including basilar skull fractures with CSF leak)
8. other infections: septicemia, pneumonia

Factors not associated with increased incidence of infection:

1. insertion of IVC in neuro intensive care unit (instead of O.R.)
2. previous IVC
3. drainage of CSF
4. use of steroids

Treatment of infection:

Removal of device if at all possible (if continued ICP monitoring is required consideration may be given to inserting a monitor at another site) and appropriate antibiotics.

TYPES OF MONITORS

1. **intraventricular catheter (IVC)**: AKA external ventricular drainage **(EVD)**, connected to an external pressure transducer via fluid-filled tubing. The standard by which others are judged (also see *Intraventricular catheter (IVC)* below)[A]

A. other options for IVCs utilize transducers tipped with fiberoptic or strain gauge devices which are located within the intraventricular catheter; in this discussion, “IVC” does not refer to this type

   A. advantages:
      1. most accurate (can be recalibrated to minimize measurement drift)[92]
      2. lower cost
      3. in addition to measuring pressure, allows therapeutic CSF drainage
   B. disadvantages
      1. may be difficult to insert into compressed or displaced ventricles
      2. obstruction of the fluid column (e.g. by blood clot) may cause inaccuracy
      3. some effort is required to check and maintain function (e.g. see *IVC problems*, page 873 and *IVC trouble shooting* on page 873)
      4. transducer must be consistently maintained at a fixed reference point relative to patient’s head (must be moved as HOB is raised/lowered)

2. **intraparenchymal monitor** (e.g. Camino labs or Honeywell/Phillips[93, 94]): similar to IVC but more expensive. Some are subject to measurement drift[95, 96], others may not be[97]
3. less accurate monitors
   A. **subarachnoid screw** (bolt): risk of infection 1%, rises after 3 days. At high ICPs (often when needed most) surface of brain may occlude lumen → false readings (usually lower than actual, may still show ≈ normal waveform)
   B. **subdural**: may utilize a fluid coupled catheter (e.g. Cordis Cup catheter), fiberoptic tipped catheter, or strain gauge tipped catheter
   C. **epidural**: may utilize a fluid coupled catheter, or fiberoptic tipped catheter (e.g. Ladd fiberoptic). Accuracy is questionable
   D. in infants, one can utilizing an open anterior fontanelle **(AF)**:
      1. **fontanometry** 98: probably not very accurate
      2. **aplanation principle**: may be used in suitable circumstances (viz.: if the fontanelle is concave with the infant upright, and convex when flat or head down) to estimate the ICP within 1 cm H_2O[75]. The infant is placed supine, and the AF is visualized and palpated while the head is raised and lowered. When the AF is flat, the ICP equals atmospheric pressure, and ICP can be estimated in cm H_2O as the distance from the AF to the point where the venous pressure is 0 (for a recumbent infant, the midpoint of the clavicle usually suffices). If the AF is not concave with the infant erect, then this method cannot be used because either the ICP exceeds the distance from the AF to the venous zero point, or the scalp may be too thick

Conversion factors: between mm Hg and cm H_2O are shown in *Eq 27-2* and *Eq 27-3* (the density of mercury is 13.6 times that of water, and CSF is fairly close to water).

$$1 \text{ mm Hg (torr)} = 1.36 \text{ cm } H_2O \qquad \textbf{Eq 27-2}$$

$$1 \text{ cm } H_2O = 0.735 \text{ mm Hg (torr)} \qquad \textbf{Eq 27-3}$$

Intraventricular catheter (IVC)

See *Types of monitors* above for some basic information.

Insertion technique

For technique to place catheter in frontal horn, see *Kocher's point* on *page 207*. The right side is usually used unless specific reasons to use the left are present (e.g. blood clot in right lateral ventricle which might occlude IVC).

Set-up

Figure 27-2 shows a typical external ventricular drainage **(EVD)** system/ventriculostomy ICP monitor. Not every system will have the same components. Note that the effect of having an opening on the top of the drip chamber (through an air-filter) is the same as having the drip nozzle open to air, and therefore as long as this filter is not wet or plugged the pressure in the IVC is regulated by the height of the nozzle (as read on the pressure scale; note that the "0" is level with the nozzle).

The external auditory canal **(EAC)** is often used as a convenient external landmark for "0" (approximates the level of the foramen of Monro). In *Figure 27-2* the drip chamber is illustrated at 8 cm above the EAC.

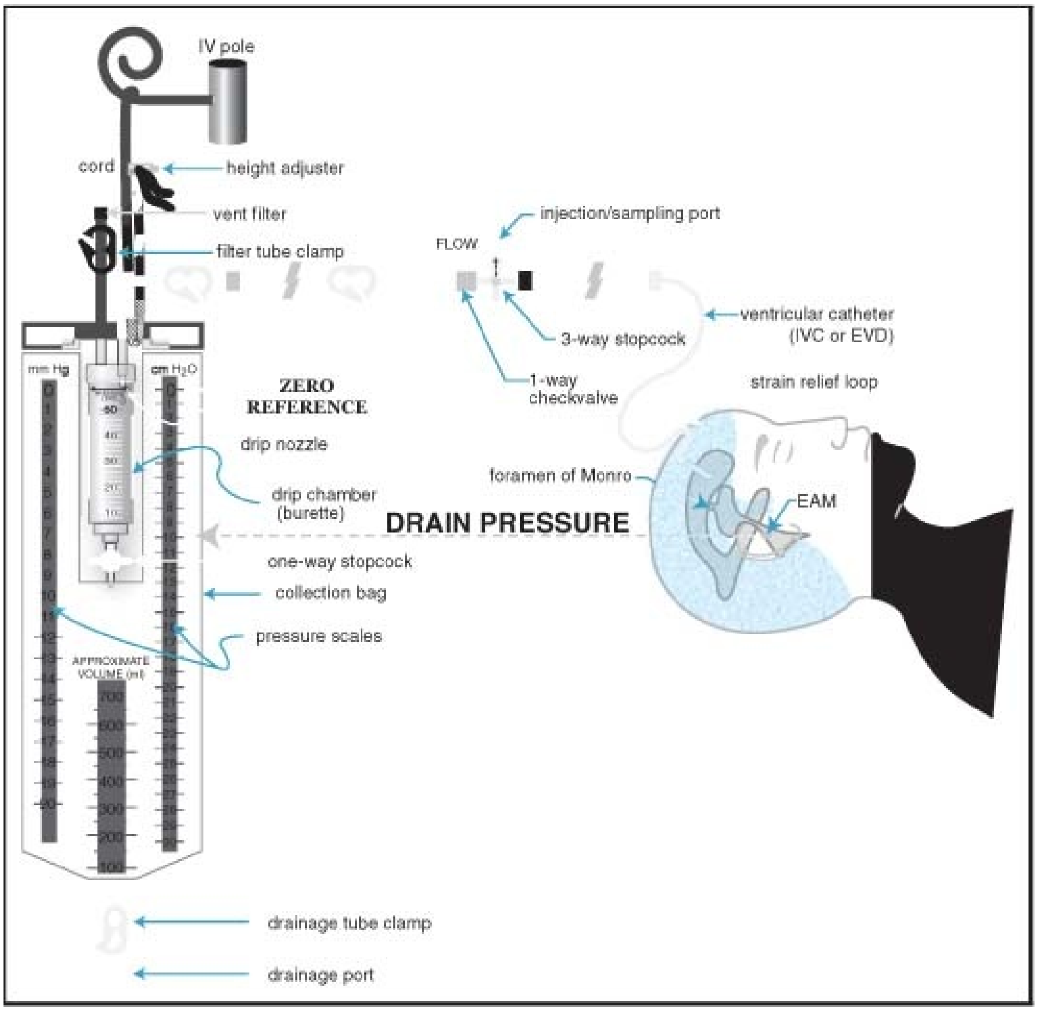


Figure 27-2 Medtronic® ventricular drainage system/ICP monitor

TYPES OF ICP WAVEFORMS

NORMAL WAVEFORMS

The normal ICP waveform (as occurs with normal blood pressure and in the absence of IC-HTN) as illustrated in *Figure 27-3* is rarely seen since ICP is usually monitored only when it is elevated. The origin of the variations seen in the normal tracing is somewhat in dispute. One explanation describes these two types of waveforms[99]:

1. small pulsations transmitted from the systemic blood pressure to the intracranial cavity
   - A. large (1-2 mm Hg) peak corresponding to the arterial systolic pressure wave, with a small dicrotic notch
   - B. this peak is followed by smaller and less distinct peaks

C. followed by a peak corresponding to the central venous "A" wave from the right atrium

2. blood pressure pulsations are superimposed on slower respiratory variations. During expiration, the pressure in the superior vena cava increases which reduces venous outflow from the cranium causing an elevation in ICP. This may be reversed in a mechanically ventilated patients, and is opposite to that in the lumbar subarachnoid space which follows the pressure in the inferior vena cava

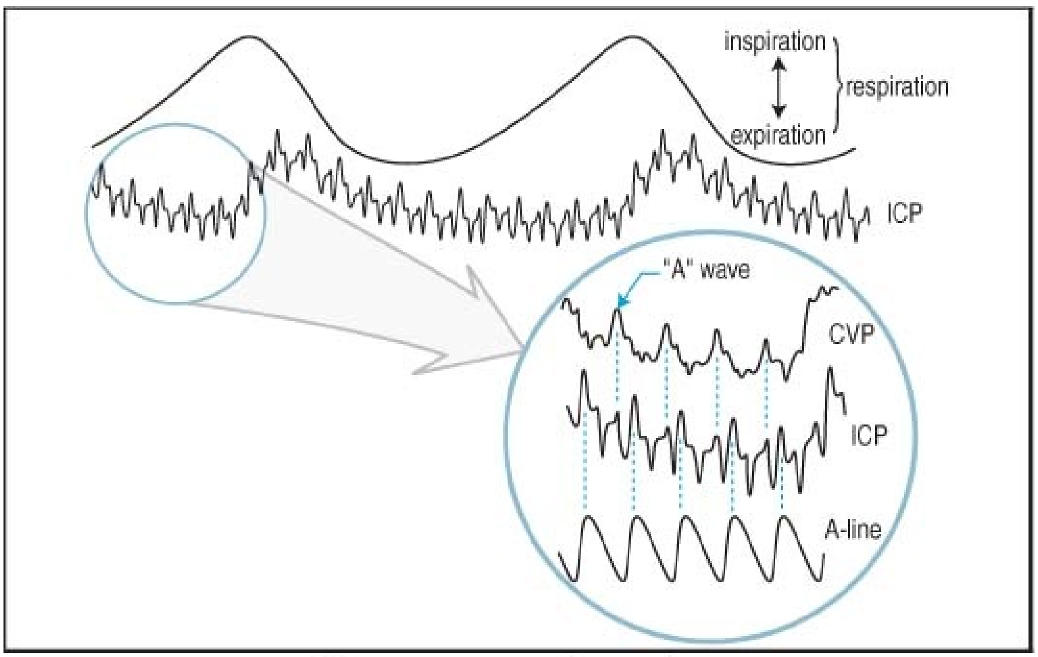


Figure 27-3 Normal ICP waveform

PATHOLOGICAL WAVEFORMS

As ICP rises and cerebral compliance decreases, the venous components disappear and the arterial pulses become more pronounced. In right atrial cardiac insufficiency, the CVP rises and the ICP waveform takes on a more "venous" or rounded appearance and the venous "A" wave begins to predominate.

A number of "pressure waves" that are more or less pathologic have been described. Currently, this classification is not considered to be of great clinical utility, with more emphasis being placed on recognizing and successfully treating elevations of ICP. Plateau waves will rarely be seen because they are usually aborted at the onset by instituting treatments outlined herein (*see page 876*). A brief description of some of these waveforms is included here for general information[100]:

1. **Lundberg A waves** AKA **plateau waves** (of Lundberg): (*see Figure 27-4*) ICP elevations ≥ 50 mm Hg for 5-20 minutes. Usually accompanied by a simultaneous increase in MAP (it is debated whether the latter is cause or effect)
2. **Lundberg B waves** AKA pressure pulses: amplitude of 10-20 mm Hg is lower than A waves. Variation with types of periodic breathing. Last 30 secs - 2 mins
3. **Lundberg C waves**: frequency of 4-8/min. Low amplitude C waves (AKA Traube-Hering waves) may sometimes be seen in the normal ICP waveform. High amplitude C-waves may be pre-terminal, and may sometimes be seen on top of plateau waves

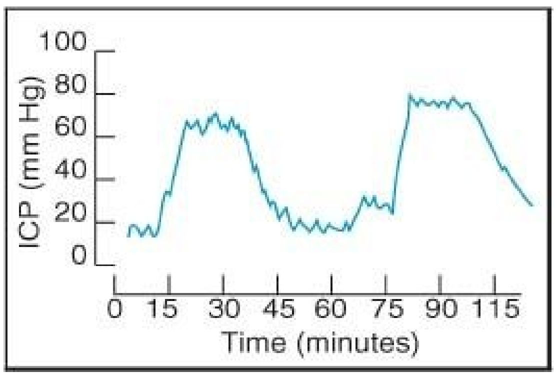


Figure 27-4 Plateau waves (Lundberg A waves)

Normal functioning of the IVC system

The system should be checked for proper functioning at least every 2-4 hours, and any time there is a change in: ICP (increase or decrease), neuro exam, or CSF output (for systems open to drainage).

1. check for presence of good waveform with respiratory variations and transmitted pulse pressures
2. IVCs: to check for patency, open the system to drain and lower the drip chamber below level of head and observe for 2-3 drops of CSF (normally do not allow more than this to drain)
3. for systems open to drainage:
   A. volume of CSF in drip chamber should be indicated every hour with a mark on a piece of tape on the drip chamber, and the volume should increase with time unless ICP is less than the height of the drip chamber (under these circumstances the system would usually not be left open to drainage).

NB: the maximum expected output from a ventriculostomy would be ≈ 450-700 ml per day in a situation where none of the produced CSF is absorbed by the patient. This is not commonly encountered. A typical amount of drainage would be ≈ 75 ml every 8 hrs

B. drip chamber should be emptied into drainage bag regularly (e.g. q 4 or 8 hours) and any time the chamber begins to get full (record volume)

4. in cases where there is a question whether the monitor is actually reflecting ICP, lowering the HOB towards 0° should increase ICP. Gentle pressure on both jugular veins simultaneously should also cause a gradual rise in ICP over 5-15 seconds that should drop back down to baseline when the pressure is released

IVC problems

The following represents some of the error or pitfalls that commonly occur with external ventricular drainage. Some also apply to ICP monitoring in general.

1. air filter on drip chamber gets wet (prevents air from passing through filter)
   A. result: fluid cannot drain freely into drip chamber (the pressure is no longer regulated by the height of the drip nozzle)
      1. if the outflow from the drip chamber is clamped, then no flow at all
      2. if the clamp on the drip chamber outlet is open, then the pressure is actually regulated by the height of the nozzle in the collection bag and not the nozzle in the drip chamber
   B. solution: if a fresh filter is available, then replace the wet one. Otherwise one must improvise (with the risk of exposing the system to contamination): e.g. replace the wet filter with a filter from an IV set, or with a sterile gauze taped over the opening
2. air filter on collection bag gets wet: this will make it difficult to empty the drip chamber into the bag
   A. this is not usually an urgent problem unless the drip chamber is full and the collection bag is distended tensely with air
   B. the filter will dry out with time and will usually start to work again
   C. if it is necessary to empty the drip chamber before the filter is dry, then using sterile technique insert a needle into the bag drainage port and decompress the bag of fluid and air

3. improper connections: a pressurized irrigation bag with or without heparinized solution should never be connected to an ICP monitor
4. changing position of head of bed: must move drip chamber up or down to keep it level with the same external landmarks (e.g. level of auditory canal):
   A. when open to drainage, this will assure the correct pressure will be maintained
   B. when opened to pressure transducer, will maintain correct zero
5. when open to drain, pressure reading from transducer is not meaningful: the pressure cannot exceed the height of the drip chamber in this situation
6. drip chamber falls to floor:
   A. overdrainage, possible seizures and/or subdural hematoma formation
   B. solution: securely tape chamber to pole, bed-rail…, check position regularly

IVC trouble shooting

See also *IVC problems* above.

1. IVC no longer works
   A. manifestation of problem:
      1. dampening or loss of normal waveform
      2. no fluid drains into drip chamber (applies only when catheter has been opened to drain)
   B. possible causes:
      1. occlusion of catheter proximal to transducer
         a. slide clamp closed or stopcock closed
         b. catheter occluded by brain particles, blood cells, protein
      2. IVC pulled out of ventricle
   C. test: temporarily lower drip nozzle and watch for 2-3 drops CSF
   D. solution:
      1. verify all clamps are open
      2. flush no more than 1.5 ml of non-bacteriostatic saline (AKA preservative-free saline) with very gentle pressure into ventricular catheter (NB: in elevated ICP the compliance of the brain is abnormally low and small volumes can cause large pressure changes)
         a. if no return then brain or clot is probably plugging catheter. If it is known that the ventricles are ≈ completely collapsed then the

IVC may be OK and CSF should still drain over time. Otherwise this is a non-functioning catheter, and if a monitor/drain is still indicated then a new catheter may need to be inserted (CT may be considered first if the status of the ventricles is not known). If catheter is clotted by intraventricular hemorrhage, rt-PA may sometimes be used[39] (*see page 1130*)

2. ICP waveform dampened
   A. possible causes:
      1. occlusion of catheter proximal to transducer: *see above*
      2. IVC pulled out of ventricle: no fluid will drain
      3. air in system:
         a. solution: allow CSF to drain and expel air
         b. caution: do not allow excessive amount of CSF to drain (may allow obstruction of catheter, subdural formation…). Do not inject fluid to flush air into brain
      4. following decompressive craniectomy: due to the fact that the monitor is no longer in a closed space, this is a normal finding in this setting

27.3.2. Adjuncts to ICP monitoring

JUGULAR VENOUS OXYGEN MONITORING

Parameters related to oxygen content of the blood in the jugular veins are global in nature and are insensitive to focal pathology, Requires retrograde placement of catheter near to the origin of the internal jugular vein at the base of the skull. Parameters that can be measured:

1. jugular venous oxygen saturation **($SjVO_2$)**: measured continuously with special fiberoptic catheter. Normal $SjVO_2$: ≥ 60%. Desaturations to < 50% suggest ischemia. Multiple desaturations (< 50%), or sustained (≥ 10 minutes) or profound desaturation episodes are associated with poor outcome[101, 102]. Sustained desaturations should prompt an evaluation for correctable etiologies: kinking of jugular vein, anemia, increased ICP, poor catheter position, CPP < 60 mm Hg, vasospasm, surgical lesion, $PaCO_2$ < 28 mm Hg. High $SjVO_2$ > 75% may indicate hyperemia or infarcted tissue and is also associated with poor outcome[103]
2. jugular vein oxygen content (CVO_2). Requires intermittent sampling of

blood

3. **arterial-jugular venous oxygen content difference ($AVdO_2$)**[104]: $AVdO_2$ > 9 ml/dl (vol%) probably indicates global cerebral ischemia[105, 106], while values < 4 ml/dl indicate cerebral **hyperemia**[107] ("luxury perfusion" in excess of the brain's metabolic requirement[106])

BRAIN TISSUE OXYGEN TENSION MONITORING ($P_{Bt}O_2$)

Monitored e.g. with Licox® probe. The likelihood of death increases with longer times of brain tissue oxygen tension **($p_{Bt}O_2$)** < 15 mm Hg or even a brief drop of $p_{Bt}O_2$ < 6108. Initial $p_{Bt}O_2$ < 10 mm Hg for > 30 minutes correlates with increased risk of death or bad outcome[109]. Also, *see PRACTICE GUIDELINE 27-13*.

Probe placement:

- TBI: assumed to be a diffuse process, often placed on <u>least</u> injured side
- SAH: placed in vascular distributions at greatest risk of vasospasm
    A. ACA (with ACA or a-comm aneurysm): standard frontal placement (≈ 2-3 cm off midline on appropriate side)
    B. MCA (with ICA or MCA aneurysm): 4.5-5.5 cm off midline
    C. ACA-MCA watershed area: 3 cm lateral to midline
- ICH: usually placed near the site of the hemorrhage

Effect of $p_{Bt}O_2$ monitoring/intervention on outcome: no randomized studies

1. in TBI[110]: goal was to maintain $p_{Bt}O_2$ > 25 mm Hg. Adding $p_{Bt}O_2$ monitoring resulted in improved outcome. May have been result of increased attentiveness ("Hawthorne effect")
2. in SAH[111]: a moving correlation coefficient (ORx) between CPP and $p_{Bt}O_2$ was used to label high ORx as disturbed autoregulation, and this value on post SAH days 5 & 6 had predictive value for delayed infarction

Management suggestions for $p_{Bt}O_2$ < 15-20 mmHg:

1. consider jugular venous O_2 saturation monitor or lactate microdialysis monitor for confirmation
2. consider CBF study to determine generalizability of $p_{Bt}O_2$ monitor reading
3. treatment: proceed to each tier as needed
    - tier 1
        1. keep body temperature < 37.5 C

2. increase CPP to > 60 mmHg (use fluids preferentially to pressors until CVP > 8 cm H_2O, then use pressors)

- tier 2
  1. increase FiO_2 to 60%
  2. increase $paCO_2$ to 45-50 mmHg
  3. transfuse PRBCs until Hgb > 10 g/dL
- tier 3
  1. increase FiO_2 to 100%
  2. consider increasing PEEP to increase PaO_2 if FiO_2 is at 100%
  3. decrease ICP to < 10 mmHg (drain CSF, mannitol, sedation…)

BEDSIDE MONITORING OF REGIONAL CBF (rCBF)

Thermal diffusion flowmetry permits continuous rCBF monitoring by assessing thermal convection due to tissue blood flow. The probe tip is inserted into the white matter of the brain. Commercially available systems include Hemedex® monitoring system (Codman) utilizing the QFLOW 500® probe which is ✖ not MRI compatible.

Probe placement: issues similar to those discussed for $p_{Bt}O_2$ (*see above*).

Readout:

1. **K value** (thermal conduction): range for white matter is **4.9-5.8** mW/cm-°C (the monitor suppresses CBF readings if the K value is outside this range)
   A. K < 4.9: the probe tip is probably out of the brain tissue or white matter - the probe should be advanced 1-2 mm
   B. K > 5.8 the tip is probably too deep, near a blood vessel, or in the ventricle or epidural or subdural space - the probe should be retracted 1-2 mm
2. **CBF**
   A. normal white matter: 18-25 ml/100g-min
      1. white matter CBF < 15: may indicate vasospasm or ischemia
      2. white matter CBF < 10: may indicate infarction
   B. normal gray matter: 67-80 ml/100g-min

Observational data: in a small study of SAH (n=5) and TBI (n=3)[112] there was good correlation between rCBF and $p_{Bt}O_2$ 91% of the time. Monitoring was not possible 36% of the time due to patient fever (wherein the system prevents monitoring).

CEREBRAL MICRODIALYSIS

Compounds assayed include: lactate, pyruvate, lactate/pyruvate ratio, glucose, glutamate, urea and electrolytes including K^+ & calcium. Some observational data:

1. lactate levels increase during episodes of $SjVO_2$ desaturation[113]
2. decreased extracellular glucose was associated with increased mortality[114]

27.3.3. Treatment measures for elevated ICP

This section presents a general protocol for treating documented (or sometimes clinically suspected) intracranial hypertension **(IC-HTN)**. Guidelines promulgated by the Brain Trauma Foundation[46, 50, 115, 116] are generally followed. Unless otherwise stated, guidelines are for adult patients (≥ 18 years age).

TREATMENT THRESHOLDS

Intracranial pressure treatment thresholds

The optimal ICP at which to begin treatment is not known. Generally accepted level: ICP ≥ 20-25 mm Hg[117]. *PRACTICE GUIDELINE 27-11* shows the Brain Trauma Foundation guideline. ✖ Caution: patients can herniate even at ICP < 20118 (depends on location of intracranial mass).

PRACTICE GUIDELINE 27-11 ICP TREATMENT THRESHOLD

Level II[117]: treatment for IC-HTN should be initiated for ICP > 20 mm Hg
Level III[117]: the need for treatment should be based on ICP in combination with clinical examination & brain CT findings

Cerebral perfusion pressure (CPP)

The optimal value for CPP has yet to be determined. The threshold for ischemia is in the 50-60 mm Hg range. Because of systemic toxicity, paradigms of maintaining CPP > 70 mm Hg have been superseded. *PRACTICE GUIDELINE 27-12* outlines current recommendations regarding CPP.

PRACTICE GUIDELINE 27-12 CEREBRAL PERFUSION PRESSURE ISSUES
Level II[119]: ✖ avoid aggressive use of fluids and pressors to maintain CPP > 70 mm Hg (because of risk of adult respiratory distress syndrome **(ARDS)**) **Level III**[119]: ✖ avoid CPP **< 50 mm Hg*** **Level III**: ancillary monitoring of CBF, oxygenation or metabolism assists CPP management

* in order to avoid CPP < 50 mm Hg, it may be best to start treatment when CPP falls < 60[119, 120]

Brain oxygenation parameters

Suggestions for treatment thresholds are shown in *PRACTICE GUIDELINE 27-13*. It remains to be determined which interventions are useful to achieve this, and whether this improves outcome.

PRACTICE GUIDELINE 27-13 BRAIN OXYGEN MONITORING
Level III[121]: jugular venous O_2 saturation **< 50%** or brain tissue oxygen tension ($p_{Bt}O_2$) **< 15 mm Hg** are treatment thresholds

ICP MANAGEMENT PROTOCOL

Table 27-20 summarizes a protocol (see *Measures to lower ICP* below for details).

Dosages are given for an average adult, unless specified as mg/kg. Treatment may be initiated prior to insertion of a monitor if there is acute neurologic deterioration or clinical signs of IC-HTN, but continued treatment requires documentation of persistent IC-HTN.

For persistent IC-HTN consider "second tier" therapies shown on *page 879*.

Additional measures which may be used to treat an acute ICP crisis are shown in *Table 27-21*.

Table 27-20 Summary of measures to control IC-HTN* Goals: keep **ICP < 20** mm Hg, and **CPP ≥ 50** mm Hg[117, 119]

Step	Rationale/Remedy
GENERAL MEASURES (should be utilized routinely)	
elevate HOB to 30-45°	↓ ICP by enhancing venous outflow, but also reduces mean carotid pressure → no net

	change in CBF
keep neck straight, avoid tight trach tape	constriction of jugular venous outflow causes ↑ ICP
avoid hypotension (SBP < 90 mm Hg)	• normalize intravascular volume • use pressors if needed
control hypertension if present	• nitroprusside if not tachycardic • beta-blocker if tachycardic (labetalol, esmolol…) • avoid overtreatment → hypotension
avoid hypoxia (PaO_2 < 60 mm Hg or O_2 sat < 90%) (maintain airway and adequate oxygenation)	hypoxia may cause further ischemic brain injury
ventilate to normocarbia ($PaCO_2$ = 35-40 mm Hg)	avoid prophylactic hyperventilation (*page 880*)
light sedation: e.g. codeine 30-60 mg IM q 4 hrs PRN	(same as *heavy sedation*, *see below*)
controversial: prophylactic hypothermia. If used, hold at target temp > 48 hrs	↓ $CMRO_2$ - efficacy not rigorously proven (*page 883*)
unenhanced head CT scan for ICP problems†	rule out surgical condition
SPECIFIC MEASURES FOR IC-HTN	
(proceed to successive steps if documented IC-HTN persists - each step is ADDED to the previous measure)	
heavy sedation (e.g. fentanyl 1-2 ml or MSO_4 2-4 mg IV q 1 hr) and/or paralysis (e.g. vecuronium 8-10mg IV)	reduces elevated sympathetic tone and HTN induced by movement, tensing abdominal musculature…
drain 3-5 ml CSF if IVC present	reduces intracranial volume
hyperventilate to $PaCO_2$ = 30-35 mm Hg ("blows off" CO_2)	↓ $PaCO_2$ → ↓ CBF → ↓ ICP
mannitol 0.25-1 gm/kg, then 0.25 mg/kg q 6 hrs, increase dose if IC-HTN persists & serum osmol ≤ 320 (NB: skip this step if hypovolemia or hypotension)	expands plasma volume, increases serum tonicity which draws fluid out of brain, may improve rheologic properties of blood
if there is "osmotic room" (i.e. serum osmol < 320) bolus with 10-20 ml of 23.4% hypertonic saline (HS)	some patients refractory to mannitol will respond to HS
hyperventilate to $PaCO_2$ = 25-30 mm Hg	monitor $SjVO_2$ (*see page 874*) or CBF if possible
If IC-HTN persists, consider unenhanced head CT† & EEG‡. Proceed to "second tier" therapy (*see page 879*).	

* see text for details (beginning on page 878). As IC-HTN subsides, carefully withdraw treatment

† if IC-HTN persists, and especially for a sudden unexplained rise in ICP or loss of previously controlled ICP, give strong consideration to repeating cranial CT to rule out a surgical condition, i.e. "clot" (SDH, EDH, or ICH) or hydrocephalus

‡ EEG to rule-out subclinical status epilepticus which is a rare cause of sustained IC-HTN

ICP MANAGEMENT PROTOCOL DETAILS

Goals of therapy:

1. keep ICP < 20 mm Hg (prevents "plateau waves" from compromising cerebral blood-flow **(CBF)** and causing cerebral ischemia and/or brain death[122])
2. keep CPP ≥ 50 mm Hg[119]. The primary goal is to control ICP, simultaneously, CPP should supported by maintaining adequate MAP[123].

SURGICAL TREATMENT

1. see surgical indications for subdural (*page 896*), epidural (*page 895*) or intraparenchymal hematoma (*page 892*) or posterior fossa mass lesions (*page 905*)
2. patients with hemorrhagic contusions ("pulped brain") showing progressive deterioration may benefit from surgically excision of portions of the contused brain tissue especially if not eloquent brain (*see page 880*)
3. decompressive craniectomy may be considered for IC-HTN that cannot be controlled medically

GENERAL CARE

Major goals:

1. avoid hypoxia (pO_2 < 60 mm Hg)
2. avoid hypotension (SBP ≤ 90 mm Hg): 67% positive-predictive value (PPV) for poor outcome (79% PPV when combined with hypoxia)[124]

Table 27-21 Measures to treat an acute ICP crisis*

Step	Rationale
check airway, position… (see general measures in *Table 27-20*). For resistant or sudden IC-HTN, consider STAT unenhanced head CT	
be sure patient is sedated and paralyzed (*see Table 27-20*)	(*see Table 27-20*)
drain 3-5 ml CSF if IVC present	↓ intracranial volume
mannitol† 1 gm/kg IV bolus or 10-20 ml of 23.4% saline	↑ plasma volume → ↑ CBF → ↓ ICP, ↑ serum osmolality → ↓ brain water
hyperventilate with Ambu® bag (always keep $PaCO_2$ > 25 mm Hg)	"blow off" (reduce) $PaCO_2$ → ↓ CBF → ↓ ICP. CAUTION: due to reduced CBF, use for no more than several minutes (*see page 880*)
pentobarbital‡ 100 mg slow IV or	sedates, ↓ ICP (NB: also myocardial depressant → ↓ MAP), treats

thiopental 2.5 mg/kg IV over 10 minutes	seizures, may be neuroprotective

* for measures to treat ICP that is trending up over a longer period, *see Table 27-20* or information starting on *page 878*

† skip this step and go to hyperventilation if hypotensive, volume depleted, or if serum osmolality > 320 mOsm/L

‡ the availability of pentobarbital in the U.S. has been reduced, and other sedatives may need to be substituted, *see page 884*

Details of general treatment measures

1. prophylaxis against steroid ulcers (if steroids are used) and Cushing's (stress) ulcers (seen in severe head injury and in increased ICP, accompanied by hypergastrinemia)[125-129] for all patients (see *Prophylaxis for stress ulcers*, page 52)
   A. elevating gastric pH: titrated antacid and/or H_2 antagonist (e.g. ranitidine 50 mg IV q 8 hrs). Avoid cimetidine if phenytoin is also being given
   B. sucralfate
2. aggressive control of fever (fever is a potent stimulus to increase CBF, and may also increase plateau waves)[122]
3. arterial line for BP monitoring and frequent ABGs
4. CVP or PA line if high doses of mannitol are needed (goal: keep patient euvolemic)
5. IV fluids
   A. choice of fluids:
      1. isolated head injury: IVF of choice is isotonic (e.g. NS + 20 mEq KCl/L)
      2. avoid hypotonic solutions (e.g. lactated ringers) which may impair cerebral compliance[130]
   B. fluid volume:
      1. provide adequate fluid resuscitation to avoid hypotension
      2. normalization of intravascular fluid volume is not detrimental to ICP
      3. although fluid restriction reduces the amount of mannitol needed to control ICP[131], the concept of "running patients dry" is obsolete[132]
      4. if mannitol is required, patient should be maintained at euvolemia
      5. also exercise caution in restricting fluids following SAH (see

Cerebral salt wasting, page 13)

6. if injuries to other systems are present (e.g. perforated viscus), they may dictate fluid management

C. pressors (e.g. dopamine) are preferable to IV fluid boluses in head injury

MEASURES TO LOWER ICP

General measures that should be routine

1. positioning:
   A. elevate HOB 30-45° (*see below*)
   B. keep head midline (to prevent kinking jugular veins)
2. light sedation: codeine 30-60 mg IM q 4 hrs PRN, or lorazepam (Ativan®) 1-2 mg IV q 4-6 hrs PRN
3. avoid hypotension (SBP < 90 mm Hg): normalize intravascular volume, support with pressors if needed
4. control HTN (in ICH, aim for patient's baseline, see *Initial management of ICH*, page 1126)
5. prevent hyperglycemia: (aggravates cerebral edema) usually present in head injury[133, 134], may be exacerbated by steroids
6. intubation: for GCS ≤ 8 or respiratory distress. Give IV lidocaine first (see *Adjunctive measures* below) and antibiotics (see *PRACTICE GUIDELINE 27-5*, page 861)
7. avoid hyperventilation: keep $PaCO_2$ at the low end of eucapnia (35 mm Hg)
8. prophylactic hypothermia: non-statistically significant trend suggests reduced mortality[135]. Maintain target temperature for > 48 hours (*see page 883*)

Measures to use for documented IC-HTN

First, check *General measures that should be routine* above. Proceed to each step if IC-HTN persists.

1. heavy sedation and/or paralysis when necessary (also assists treatment of HTN) e.g. when patient is agitated, or to blunt the elevation of ICP that occurs with certain maneuvers such as moving the patient to CT table. Caution: with heavy sedation or paralysis, the ability to follow the

neurologic exam is lost (follow ICPs)

A. for heavy sedation (intubation recommended to avoid respiratory depression → elevation of $PaCO_2$ → ↑ ICP): e.g. one of the following:

1. MSO_4: ***Rx*** 2-4 mg/hr IV drip
2. fentanyl: ***Rx*** 1-2 ml IV q 1 hr (or 2-5 µg/kg/hr IV drip)
3. sufentanil: ***Rx*** 10-30 µg test dose, then 0.05 -2 µg/kg/hr IV drip
4. midazolam (Versed®): ***Rx*** 2 mg test dose, then 2-4 mg/hr IV drip
5. propofol drip (*see page 24*): 0.5 mg/kg test dose, then 20-75 µg/kg/min IV drip ✖ avoid high-dose propofol (do not exceed 83 µg/kg/min)
6. "low dose" pentobarbital (adult: 100 mg IV q 4 hrs; peds: 2-5 mg/kg IV q 4 hrs)

B. paralysis (intubation mandatory): e.g. vecuronium 8-10 mg IV q 2-3 hrs

2. CSF drainage (when IVC is being utilized to measure ICP): 3-5 ml of CSF should be drained with the drip chamber at ≤ 10 cm above EAC. Works immediately by removal of CSF (reducing intracranial volume) and possibly by allowing edema fluid to drain into ventricles[136] (latter point is controversial)
3. "**osmotic therapy**" when there is evidence of IC-HTN:

A. mannitol (also *see below*) 0.25-1 gm/kg bolus (over < 20 mins) followed by 0.25 gm/kg IVP (over 20 min) q 6 hrs PRN ICP > 20. Recent literature suggests that 1.4 gm/kg initial dose is more effective. May "alternate" with: furosemide (Lasix®) (also *see below*): adult 10-20 mg IV q 6 hrs PRN ICP > 20. Peds: 1 mg/kg, 6 mg max IV q 6 hrs PRN ICP > 20

B. keep patient euvolemic to slightly hypervolemic

C. if IC-HTN persists and serum osmolarity is < 320 mOsm/L, increase mannitol up to 1 gm/kg, and shorten the dosing interval

D. if ICP remains refractory to mannitol, consider hypertonic saline, either continuous 3% saline infusion or as bolus of 10-20 ml of 23.4% saline (D/C after ≈ 72 hours to avoid rebound edema)

E. hold osmotic therapy if serum osmolarity is **≥ 320 mOsm/L** (higher tonicity may have no advantage and risks renal dysfunction (*see below*)) or SBP < 100

4. hyperventilation **(HPV)** to **$PaCO_2$ = 30-35 mm Hg** (for details, *see below*)

A. ✖ do not use prophylactically
B. ✖ avoid aggressive HPV ($PaCO_2 \leq 25$ mm Hg) at all times
C. use only for
   1. short periods for acute neurologic deterioration
   2. or chronically for documented IC-HTN unresponsive to sedation, paralytics, CSF drainage and osmotic therapy
D. avoid HPV during the first 24 hrs after injury if possible

5. ✖ steroids: the routine use of glucocorticoids is not recommended for treatment of patients with head injuries (*see below*)

"Second tier" therapy for persistent IC-HTN

If IC-HTN remains refractory to the above measures, and especially if there is loss of previously controlled ICP, strong consideration should be given to repeating a head CT to rule out a surgical condition before proceeding with "second tier" therapies which are either effective but with significant risks (e.g. high-dose barbiturates), or are unproven in terms of benefit on outcome. Also consider an EEG to rule-out status epilepticus that is not clinically evident (*see page 405* for treatment measures for status epilepticus; some medications are effective for both seizures and IC-HTN, e.g. pentobarbital, propofol…).

1. high dose barbiturate therapy: initiate if ICP remains > 20-25 mm Hg (see *High-dose barbiturate therapy*, page 883)
2. hyperventilate to $PaCO_2$ = 25-30 mm Hg. Monitoring $SjVO_2$, $AVdO_2$, and/or CBF is recommended (*see below*)
3. hypothermia[137, 138]: patients must be monitored for a drop in cardiac index, thrombocytopenia, elevated creatinine clearance, and pancreatitis. Avoid shivering which raises ICP[138]
4. decompressive surgery:
   A. decompressive craniectomy removal of portion of calvaria[139]. Controversial (may enhance cerebral edema formation[140]). Craniectomy decreased ICP to < 20 mm Hg in 85%[141] regardless of pupillary response to light, timing of craniectomy, brain shift and age. Outcomes were improved when IC-HTN responded[82, 141, 142]. Further randomized trials are indicated. Early decompressive craniectomy may be considered in patients undergoing emergent surgery (for fracture, EDH, SDH…)[143]. Flap must be at least 12 cm in diameter, and duraplasty is mandatory. Also, see *Hemicraniectomy for malignant*

MCA territory infarction, page 1022

B. removal of large areas of contused hemorrhagic brain (makes room immediately; removes region of disrupted BBB). If contused, consider temporal tip lobectomy (no more than 4-5 cm on dominant side, 6-7 cm on non-dominant) (total temporal lobectomy[144] is probably too aggressive) or frontal lobectomy. Has not shown great therapeutic promise

5. lumbar drainage: showing some promise. Watch for “cerebral sag”
6. hypertensive therapy

Adjunctive measures

1. lidocaine: 1.5 mg/kg IVP (watch for hypotension, reduce dose if necessary) at least one minute before endotracheal intubation or suctioning. Blunts the rise in ICP as well as tachycardia and systemic HTN (based on patients with brain tumors undergoing intubation under light barbiturate-nitrous oxide anesthesia; extrapolation to trauma patients is unproven)[145]
2. high frequency (jet) ventilation: consider if high levels of positive end-expiratory pressure **(PEEP)** are required[146] (NB: patients with reduced lung compliance, e.g. pulmonary edema, transmit more of PEEP through lungs to thoracic vessels and may raise ICP). PEEP $\leq$ 10 cm H_2O does not cause clinically significant increases in ICP[147]. Higher levels of PEEP > 15-20 are not recommended. Also, rapid elimination of PEEP may cause a sudden increase in circulating blood volume which may exacerbate cerebral edema and also elevate ICP

Details of some measures outlined above

Elevating head of bed ***(HOB)***

Early data indicated that keeping the HOB at 30-45° optimized the trade-off between the following two factors as the HOB is elevated: reducing ICP (by enhancing venous outflow and by promoting displacement of CSF from the intracranial compartment to the spinal compartment) and reducing MAP (and thus CPP) at the level of the carotid arteries.

Recent data[148] indicate that although mean carotid pressure **(MCP)** is reduced, the ICP is also reduced and the CBF is unaffected by elevating the HOB to 30°. The onset of action of raising the HOB is immediate.

Hyperventilation

Intraarterial carbon dioxide ($PaCO_2$) is the most potent cerebrovascular vasodilator. Hyperventilation **(HPV)** lowers ICP by reducing $PaCO_2$ which causes cerebral vasoconstriction, thus reducing the cerebral blood volume **(CBV)**[149]. Of concern, vasoconstriction also lowers cerebral blood flow **(CBF)** which could produce focal ischemia in areas with preserved cerebral autoregulation as a result of shunting[150, 151]. However, ischemia does not necessarily follow as the O_2 extraction fraction **(OEF)** may also increase, up to a point[152].

✖ Hyperventilation **(HPV)**, is to be used in moderation only in specific situations[50] (*see below*). *Prophylactic*[A] HPV may actually be associated with a worse outcome[154]. When indicated, use HPV only to $PaCO_2$ = 30-35 mm Hg (see *Caveats for hyperventilation* below). CBF in severe head trauma patients is already about half of normal during the first 24 hrs after injury[155-158]. In one study, the use of HPV to $PaCO_2$ = 30 mm Hg within 8-14 hrs of severe head injury did not impair *global* cerebral metabolism[152], but *focal* changes were not studied. Hyperventilation to $PaCO_2$ < 30 mm Hg further reduces CBF, but does not consistently reduce ICP and may cause loss of cerebral autoregulation[106]. If carefully monitored, there may be occasion to use this. A summary of the ranges of $PaCO_2$ and the recommendations is shown in *Table 27-22*.

A. *prophylactic* HPV implies cases where there are no clinical signs of IC-HTN and where IC-HTN unresponsive to other measures has not been documented by ICP monitoring

PRACTICE GUIDELINE 27-14 HYPERVENTILATION FOR ICP MANAGEMENT*

Level I[153]: in the absence of IC-HTN, chronic prolonged hyperventilation **(HPV)** ($PaCO_2 \leq 25$ mm Hg) should be avoided

Level II[53]: *prophylactic* hyperventilation ($PaCO_2 \leq 25$ mm Hg) is not recommended

Level III

- HPV may be necessary for brief periods when there is acute neurologic deterioration, or for longer periods if there is IC-HTN refractory to sedation, paralysis, CSF drainage and osmotic diuretics[153]

- HPV should be avoided ≤ 24 hrs after head injury[53]
- if HPV is used, jugular venous oxygen saturation ($SjVO_2$) (*see* *page 874*) or $P_{br}O_2$ (*see* *page 874*) should be measured to monitor brain O_2 delivery[53]

* for prophylactic hyperventilation, see *PRACTICE GUIDELINE 27-6*, page 861

Reducing $PaCO_2$ from 35 to 29 mm Hg lowers ICP 25-30% in most patients. Onset of action: ≤ 30 seconds. Peak effect at ≈ 8 mins. Duration of effect is occasionally as short as 15-20 mins. Effect may be blunted by 1 hour (based on patients with intracranial tumors), after which it is difficult to return to normocarbia without rebound elevation of ICP[159, 160]. Thus, HPV must be weaned slowly[122].

Table 27-22 Summary of recommendations for $PaCO_2$ following head trauma (*see text* for details)

$PaCO_2$ (mm Hg)	Description
35-40	**normocarbia**. Use routinely
30-35	**hyperventilation**. Do not use prophylactically. Use only as follows: briefly for clinical evidence of IC-HTN (neurologic deterioration) or chronically for documented IC-HTN unresponsive to other measures
25-30	**augmented hyperventilation**. A second tier treatment. Use only when other methods fail to control IC-HTN. Additional monitoring recommended to R/O cerebral ischemia
< 25	**aggressive hyperventilation**. No documented benefit. Significant potential for ischemia

Indications for hyperventilation (HPV)

1. HPV for brief periods (minutes) at the following times
   A. prior to insertion of ICP monitor: if there are clinical signs of IC-HTN (see *Table 27-14*, page 861)
   B. after insertion of a monitor: if there is a sudden increase in ICP and/or acute neurologic deterioration, HPV may be used while evaluating patient for a treatable condition (e.g. delayed intracranial hematoma)
2. HPV for longer periods: when there is documented IC-HTN unresponsive to sedation, paralytics, CSF drainage (when available) and osmotic diuretics
3. HPV may be appropriate for IC-HTN resulting primarily from hyperemia (*see* *page 902*)

Caveats for hyperventilation

1. avoid during the first 5 days after head injury if possible (especially first 24 hrs)
2. do not use prophylactically (i.e. without appropriate indications, *see above*)
3. if documented IC-HTN is unresponsive to other measures, hyperventilate only to $PaCO_2$ = 30-35 mm Hg
4. if prolonged HPV to $PaCO_2$ of 25-30 mm Hg is deemed necessary, consider monitoring $SjVO_2$, $AVdO_2$, or CBF to rule-out cerebral ischemia (*see page 874*)
5. do not reduce $PaCO_2$ < 25 mm Hg (except for very brief periods of a few minutes)

MANNITOL

PRACTICE GUIDELINE 27-15 MANNITOL IN SEVERE TRAUMATIC BRAIN INJURY

Level II[54, 161]

- mannitol is effective for control of IC-HTN after severe TBI*
- intermittent boluses may be more effective than continuous infusion
- effective doses range from 0.25-1 gm/kg body weight
- avoid hypotension (SBP < 90 mm Hg)

Level III[161]

- indications: signs of transtentorial herniation or progressive neurological deterioration not attributable to systemic pathology
- euvolemia should be maintained (hypovolemia should be avoided) by fluid replacement. An indwelling urinary catheter is essential
- serum osmolarity should be kept < 320 mOsm when there is concern about renal failure

* current information did not allow recommendations regarding hypertonic saline to be made[54]

The mechanism(s) by which mannitol provides its beneficial effects is still controversial, but probably includes some combination of the following

1. lowering ICP
   A. immediate plasma expansion[162-164]: reduces the hematocrit and blood

viscosity (improved rheology) which increases CBF and O_2 delivery. This reduces ICP within a few minutes, and is most marked in patients with CPP < 70 mm Hg

B. osmotic effect: increased serum tonicity draws edema fluid from cerebral parenchyma. Takes 15-30 minutes until gradients are established[162]. Effect lasts 1.5-6 hrs, depending on the clinical condition[50, 165, 166]

2. supports the microcirculation by improving blood rheology (*see above*)
3. possible free radical scavenging[167]

With bolus administration, onset of ICP lowering effect occurs in 1-5 minutes; peaks at 20-60 minutes. When urgent reduction of ICP is needed, an initial dose of 1 gm/kg should be given over 30 minutes. When long-term reduction of ICP is intended, the infusion time should be lengthened to 60 minutes[168] and the dose reduced (e.g. 0.25-0.5 gm/kg q 6 hrs).

Cautions with mannitol

1. mannitol opens the BBB, and mannitol that has crossed the BBB may draw fluid into the CNS (this may be minimized by repeated bolus administration vs. continuous infusion[163, 169]) which can aggravate vasogenic cerebral edema[170]. Thus, when it is time to D/C mannitol, it should be tapered to prevent ICP rebound[168]
2. caution: corticosteroids + phenytoin + mannitol may cause hyperosmolar nonketotic state with high mortality[122]
3. excessively vigorous bolus administration may → HTN and if autoregulation is defective → increased CBF which may promote herniation rather than prevent it[171]
4. high doses of mannitol carries the risk of acute renal failure (acute tubular necrosis), especially in the following[76, 172]: serum osmolarity > 320 mOsm/L, use of other potentially nephrotoxic drugs, sepsis, pre-existing renal disease
5. large doses prevents diagnosing DI by use of urinary osmols or SG (*see page 16*)
6. because it may further increase CBF[173], the use of mannitol may be deleterious when IC-HTN is due to hyperemia (*see page 902*)

Furosemide

The use of furosemide (Lasix®) has been advocated, but little data exists to support this[50]. Loop acting diuretics may reduce ICP[174] by reducing cerebral edema[175] (possibly by increasing serum tonicity), and may also slow the production of CSF[176]. They also act synergistically with mannitol[177] (see *Mannitol* above).

Rx: 10-20 mg IV q 6 hrs, may be alternated with mannitol such that the patient receives one or the other q 3 hrs. Hold if serum osmolarity > 320 mOsm/L.

*Hypertonic saline **(HS)***

May reduce ICP in patients refractory to mannitol[178, 179], although no improvement in outcome over mannitol has been demonstrated[179, 180]. Potentially deleterious effect on stroke penumbra in animal studies. Studies[181, 182] not adequate to make recommendations regarding use[54].

Rx: Continuous infusion: 3% saline at 25-50 ml/hr may be given through a peripheral IV. Bolus: 10-20 ml of 7.5-23.4% saline must be given through a central line. HS should be discontinued after ≈ 72 hours to avoid rebound edema[179]. Hold if serum osmolarity > 320 mOsm/L.

Prophylactic hypothermia

PRACTICE GUIDELINE 27-16 Prophylactic hypothermia

Level III[135]: *prophylactic* hypothermia:
- improves the chances of having a moderate to good outcome (4-5 on the Glasgow Outcome Score, *see page 1183*) at the end of the follow-up period when target temperatures of 32-35° C* (91.4-95° F) were used
- showed a non-significant trend suggesting that it lowers mortality when the target temperature is maintained for > 48 hrs†

* no clear relationship was found for cooling duration or rewarming rate

† the actual target temperature and rewarming rate did not influence mortality

Steroids

PRACTICE GUIDELINE 27-17 Glucocorticoids in severe head injury

Level I[183]: the use of glucocorticoids (steroids) is not recommended for improving outcome or reducing ICP in patients with severe TBI (except in patients with known depletion of endogenous adrenal hormones[184, 185]). High-dose methylprednisolone is associated with increased mortality and is contraindicated[183]

Although glucocorticoids reduce **vasogenic cerebral edema** (e.g. surrounding brain tumors) and may be effective in lowering ICP in pseudotumor cerebri, they have little effect on **cytotoxic cerebral edema** which is more prevalent following trauma (see *Cerebral edema*, page 109).

Significant side effects may occur[186] including coagulopathies, hyperglycemia[187] with its undesirable effect on cerebral edema (see *Possible deleterious side effects of steroids*, page 33), and increased incidence of infection. High-dose methylprednisolone is associated with increased mortality[188].

Non-glucocorticoid steroids (e.g. 21-aminosteroids, AKA lazaroids, including tirilazad[189, 190]) and the synthetic glucocorticoid triamcinolone[191] have also failed to show overall benefit.

27.3.3.1. High-dose barbiturate therapy

PRACTICE GUIDELINE 27-18 BARBITURATES IN SEVERE HEAD INJURY

Level II[192]: ✖ *prophylactic* use of barbiturates for burst suppression EEG is <u>not</u> recommended

Level II[192]: high-dose barbiturates are recommended for IC-HTN refractory to maximal medical and surgical ICP lowering therapy. Patients should be hemodynamically stable before and during treatment

Theoretical benefits of barbiturates in head injury derive from vasoconstriction in normal areas (shunting blood to ischemic brain tissue), decreased metabolic demand for O_2 ($CMRO_2$) with accompanying reduction of CBF, free radical scavenging, reduced intracellular calcium, and lysosomal stabilization[193]. There is little question that barbiturates lower ICP, even when other treatments have failed[194], but regarding outcome, studies have shown both benefits[195, 196] and lack of same[197, 198]. Patients that do respond have a lower

mortality (33%) than those in whom ICP control could not be accomplished (75%)[196].

The limiting factor for therapy is usually hypotension due to barbiturate induced reduction of sympathetic tone[199 (p 354)] (causing peripheral vasodilatation) and direct mild myocardial depression. Hypotension occurs in ≈ 50% of patients in spite of adequate blood volume and use of dopamine[197].

NB: the ability to follow the neurologic exam is lost, and one must follow ICP.

"Barbiturate coma" vs. high-dose therapy: If barbiturates are given until there is burst suppression on EEG, this is considered true "barbiturate coma". This results in near maximal reductions in $CMRO_2$ and CBF[50]. However, most regimens should technically be called "high dose intravenous therapy" since they simply try to establish target serum barbiturate levels (e.g. 3-4 mg% for pentobarbital), even though there is poor correlation between serum level, therapeutic benefit, and systemic complications[50].

Adjunctive measures to administration of high-dose barbiturates:

1. consider a Swan-Ganz (PA) catheter placed during the first hour of loading dose
2. high-dose barbiturates cause paralytic ileus: therefore NG tube to suction & IV hyperalimentation are usually needed

INDICATIONS

The use of barbiturates should be reserved for situations where the ICP cannot be controlled by the previously outlined measures[196], as there is evidence that prophylactic barbiturates do not favorably alter outcome, and are associated with significant side effects, mostly hypotension[197], that can cause neurologic deterioration.

CHOICE OF AGENTS

A number of agents have been studied, however, there is inadequate data to recommend one drug over another. The most information is available on pentobarbital (*see below*). Alternative agents which have not been as well studied: thiopental (*see below*), phenobarbital (*see page 413*) & propofol (*see page 885*).

pentobarbital (Nembutal®) **DRUG INFO**

Pentobarbital has a fast onset (full effects within ≈ 15 minutes), short duration of action (3-4 hrs), and a half life of 15-48 hrs.

Protocols for pentobarbital therapy in adults

There are many protocols. A simple one from a randomized clinical trial[200]:

- loading dose:
  - A. pentobarbital 10 mg/kg IV over 30 minutes
  - B. then 5 mg/kg q 1 hr **x** 3 doses
- maintenance: 1 mg/kg/hr

A more elaborate protocol:

1. loading dose: pentobarbital 10 mg/kg/hr IV over 4 hrs as follows:
   - A. FIRST HOUR: 2.5 mg/kg slow IVP q 15 min **x** 4 doses (total: 10 mg/kg in first hr), follow BP closely
   - B. next 3 hours: 10 mg/kg/hr continuous infusion (put 2500 mg in 250 ml of appropriate IVF, run at **K** ml/hr **x** 3 hrs (**K** = patient's weight in kg))
2. maintenance: 1.5 mg/kg/hr infusion (put 250 mg in 250 ml IVF and run at 1.5 **x** **K** ml/hr)
3. check serum pentobarbital level 1 hr after loading dose completed; usually 3.5-5.0 mg%
4. check serum pentobarbital level q day thereafter
5. if level ever > 5 mg% and ICP acceptable, reduce dose
6. baseline brain stem auditory evoked response **(BAER)** early in treatment. May be omitted on clinical grounds. Repeat BAER if pentobarbital level ever > 6 mg%. Reduce dose if BAER deteriorates (caution: hemotympanum may interfere with BAER)

Table 27-23 CNS effects of various pento-barbital levels*

Degree of CNS depression	mg%	µg/ml
level for valid brain death exam	≤ 1	≤ 10
sedated, relaxed, easily aroused	0.05-0.3	0.5-3
heavy sedation, difficult to arouse, respiratory depression	2	20

"coma" level (burst suppression occurs in most patients)	5	50

* levels reported are for intolerant patients; there is significant variability between patients and tolerant patients may not be sedated even at levels as high as 100 µg/ml

7. goal: ICP < 24 mm Hg and pentobarbital level 3-5 mg%. Consider discontinuing pentobarbital due to ineffectiveness if ICP still > 24 with adequate drug levels **x** 24 hrs
8. if ICP < 20 mm Hg, continue treatment **x** 48 hrs, then taper dose. Backtrack if ICP rises

Neuro function takes ≈ 2 days off pentobarbital to return (*see Table 27-23*). Level should be ≈ ≤ 10 µg/ml before brain death exam is valid.

thiopental (Pentothal®) **DRUG INFO**

May be useful when a rapidly acting barbiturate is needed (e.g. intra-op) or when large doses of pentobarbital are not available. One of many protocols follows (note: thiopental has not been as well studied for this indication, but is theoretically similar to pentobarbital[201, 202]):

1. loading dose: thiopental 5 mg/kg (range: 3-5) IV over 10 minutes
2. follow with continuous infusion of 5 mg/kg/hr (range: 3-5) for 24 hours
3. may need to rebolus with 2.5 mg/kg as needed for ICP control
4. after 24 hours, fat stores become saturated, reduce infusion to 2.5 mg/kg/hr
5. titrate to control ICP or use EEG to monitor for electrocerebral silence
6. "therapeutic" serum level: 6-8.5 mg/dl

propofol (Diprivan®) **DRUG INFO**

PRACTICE GUIDELINE 27-19 PROPOFOL IN SEVERE HEAD INJURY

Level II[192]: propofol may control ICP after several hours of dosing, but it does not improve mortality or ✖ month outcome. ✖ Caution: high-dose propofol (total dose > 100 mg/kg for > 48 hrs) can cause significant morbidity

Rx: 0.5 mg/kg test dose, then 20-75 µg/kg/min infusion. Increase by 5-10 µg/kg/min q 5-10 minutes PRN ICP control (do not exceed 83 µg/kg/min = 5 mg/kg/hr).

SIDE EFFECTS: include Propofol Infusion Syndrome (*see page 25*). Use with caution at doses > 5 mg/kg/hr or at any dose for > 48 hrs.

27.4. Skull fractures

Table 27-24 shows some differentiating features to distinguish linear skull fractures. See also *Indications for CT and admission criteria for TBI* on page 856.

90% of pediatric skull fractures are linear and involve the calvaria.

Diastatic fractures extend into and separate sutures. More common in young children[203].

Table 27-24 Differentiating linear skull fractures from normal plain film findings

Feature	Linear skull fracture	Vessel groove	Suture line
density	dark black	grey	grey
course	straight	curving	follows course of known suture lines
branching	usually none	often branching	joins other suture lines
width	very thin	thicker than fracture	jagged, wide

27.4.1. Depressed skull fractures

Classified as either closed (**simple fracture**) or open (**compound fracture**).

ADULT

See *PRACTICE GUIDELINE 27-20* for surgical management guidelines. Some additional observations regarding surgery to elevate a depressed skull fracture in an adult:

1. consider surgery for depressed skull fractures with deficit referable to underlying brain
2. ✖ more conservative treatment is recommended for fractures overlying a major dural venous sinus[A]

A. exception: depressed fractures overlying and depressing one of the dural sinuses may be dangerous to elevate, and if the patient is neurologically intact, and no indication for operation (e.g. CSF leak mandates surgery) may be best managed conservatively

PRACTICE GUIDELINE 27-20 SURGICAL MANAGEMENT OF DEPRESSED SKULL FRACTURES

Indications for surgery

Level III[204]:

- open (compound) fractures
  A. surgery for fractures depressed > thickness of calvaria and those not meeting criteria for nonsurgical management listed below
  B. nonsurgical management may be considered if
    1. there is no evidence (clinical or CT) of dural penetration (CSF leak, intradural pneumocephalus on CT…)
    2. *and* no significant intracranial hematoma
    3. *and* depression is < 1 cm
    4. *and* no frontal sinus involvement
    5. *and* no wound infection or gross contamination
    6. *and* no gross cosmetic deformity
- closed (simple) depressed fractures: may be managed surgically or nonsurgically

Timing of surgery

Level III[204]: early surgery to reduce risk of infection

Surgical methods

Level III[204]:

- elevation and debridement are recommended
- option: if there is no evidence of wound infection, primary bone replacement
- antibiotics should be used for all compound depressed fractures

There is no evidence that elevating a depressed skull fracture will reduce the

subsequent development of posttraumatic seizures[205], which are probably more related to the initial brain injury.

PEDIATRIC[206]

Most common in frontal and parietal bones. One third are closed, and these tend to occur in younger children as a result of the thinner, more deformable skull. Open fractures tended to occur with MVAs, closed fractures tended to follow accidents at home. Dural lacerations are more common in compound fractures.

Simple depressed skull fractures

No difference in outcome (seizures, neurologic dysfunction or cosmetic appearance) in surgical vs. nonsurgical treatment. In the younger child, remodelling of the skull as a result of brain growth tends to smooth out the deformity.

Indications for surgery for pediatric simple depressed skull fracture:

1. definite evidence of dural penetration
2. persistent cosmetic defect in the older child after the swelling has subsided
3. ± focal neurologic deficit related to the fracture (this group has a higher incidence of dural laceration, although it is usually trivial)

"Ping-pong ball" fractures[207]

A green-stick type of fracture → caving in of a focal area of the skull as in a crushed area of a ping-pong ball. Usually seen only in the newborn due to the plasticity of the skull.

Indications for surgery

No treatment is necessary when these occur in the temporoparietal region in the absence of underlying brain injury as the deformity will usually correct as the skull grows.

1. radiographic evidence of intraparenchymal bone fragments
2. associated neurologic deficit (rare)
3. signs of increased intracranial pressure
4. signs of CSF leak deep to the galea
5. difficulty with long-term follow-up

Technique

Frontally located lesions may be corrected for cosmesis by a small linear incision behind the hairline, opening the cranium adjacent to the depression, and pushing it back out e.g. with a Penfield #3 dissector.

Booking the case - craniotomy: for depressed skull fracture

Also see defaults & disclaimers (*page v*).

1. position: (depends on location of the fracture)
2. post-op: ICU
3. blood: type & screen (for severe fractures: type and cross 2 U PRBC)
4. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery in the area of the skull fracture to bone fragments that may have been displaced, to repair the covering of the brain, to remove any foreign material that can be identified and any permanently damaged brain tissue (i.e. dead brain tissue), remove any blood clot and stop any bleeding identified, possible placement of intracranial pressure monitor. If a large opening has to be left in the skull, it may require surgery to correct in a number of months (3 or more)
   B. alternatives: nonsurgical management
   C. complications: (usual craniotomy complications - *see page v*) *plus* any permanent brain injury that has already occurred is not likely to recover, seizures may occur (with or without the surgery), hydrocephalus, infection (including delayed infection/abscess)

Technical considerations of surgery

Surgical goals (modified[208])

1. debridement of skin edges
2. elevation of bone fragments
3. repair of dural laceration
4. debridement of devitalized brain
5. reconstruction of the skull
6. skin closure

Techniques

1. with open (compound) contaminated fractures, it may be necessary to excise depressed bone. In these cases or when air sinuses are involved, to minimize the risk of infecting the flap, some surgeons follow the patient for 6-12 months to rule out infection before performing a cosmetic cranioplasty. There has been no documented increase in infection with replacement of bone fragments; soaking the fragments in povidone-iodine has been recommended[208]
2. elevating the bone may be facilitated by drilling burr holes around the periphery and either using rongeurs or craniotome to excise the depressed portion
3. in cases where laceration of a major dural sinus is suspected and surgery is mandated, adequate preparation must be made for dural sinus repair[209] (NB: the SSS is often to the right of the sagittal suture - *see page 87*)
   A. prepare for massive blood loss
   B. have small Fogarty catheter ready to temporarily occlude sinus
   C. have dural shunt ready (Kapp-Gielchinsky shunt, if available, has an inflatable balloon at both ends)
   D. prep out saphenous vein area for vein graft
   E. bone fragments that may have lacerated sinus should be removed last

27.4.2. Basal skull fractures

Most basal (AKA basilar) skull fractures **(BSF)** are extensions of fractures through the cranial vault.

DIAGNOSIS

Radiographic diagnosis

CT scan is often poor for directly demonstrating BSF. Plain skull x-rays and clinical criteria (*see below*) are usually more sensitive. Sensitivity of CT diagnosis can be increased by the use of bone windows together with thin cuts ($\leq$ 5 mm) and coronal images. BSF appear as linear lucencies through the skull base.

Indirect radiographic findings (on CT or plain films) that suggest BSF include: pneumocephalus (diagnostic of BSF in the absence of an open fracture

of the cranial vault), air/fluid level within or opacification of air sinus with fluid (suggestive). Other related findings include: fractures of the cribriform plate or orbital roof.

Clinical diagnosis

Some of these signs may take several hours to develop. Signs include:

1. CSF otorrhea or rhinorrhea
2. hemotympanum or laceration of external auditory canal
3. postauricular ecchymoses (Battle's sign)
4. periorbital ecchymoses (raccoon's eyes) in the absence of direct orbital trauma, especially if bilateral
5. cranial nerve injury:
   A. VII and/or VIII: usually associated with temporal bone fracture
   B. olfactory nerve (Cr. N. I) injury: often occurs with anterior fossa BSF and results in anosmia, this fracture may extend to the optic canal and cause injury to the optic nerve (Cr. N. II)
   C. VI injury: can occur with fractures through the clivus (*see below*)

Severe basilar skull fractures may produce shearing injuries to the pituitary gland.

TREATMENT

NG tubes: ✖ Caution: cases have been reported where an NG tube has been passed intracranially[210-212] and is associated with fatal outcome in 64% of cases. Possible mechanisms include: a cribriform plate that is thin (congenitally or due to chronic sinusitis) or fractured (due to a frontal basal skull fracture or a comminuted fracture through the skull base).

Suggested contraindications to blind placement of an NG tube include: trauma with possible basal skull fracture, ongoing or history of previous CSF rhinorrhea, meningitis with chronic sinusitis.

Prophylactic antibiotics: The routine use of prophylactic antibiotics is controversial. This remains true even in the presence of a CSF fistula (see *CSF fistula (cranial)*, page 300). However, most ENT physicians recommend treating fractures through the nasal sinuses as open contaminated fractures, and they use broad spectrum antibiotics (e.g. ciprofloxacin) for 7-10 days.

Treatment of the BSF: Most do not require treatment by themselves. However,

conditions that may be associated with BSF which may require specific management include:

1. “traumatic aneurysms”[213] (see *Traumatic aneurysms*, page 1081)
2. posttraumatic carotid-cavernous fistula (see *Carotid-cavernous fistula*, page 1113)
3. CSF fistula: operative treatment may be required for persistent CSF rhinorrhea (see *CSF fistula (cranial)*, page 300)
4. meningitis or cerebral abscess: may occur with BSF into air sinuses (frontal or mastoid) even in the absence of an identifiable CSF leak. May even occur many years after the BSF was sustained (see *Post craniospinal trauma meningitis (post-traumatic meningitis)*, page 344)
5. cosmetic deformities
6. posttraumatic facial palsy (see *Temporal bone fractures* below)

TEMPORAL BONE FRACTURES

Although often mixed, there are two basic types of temporal bone fractures:

1. longitudinal fracture: more common (70-90%). Usually through petro-squamosal suture, parallel to and through EAC. Can often be diagnosed on otoscopic inspection of the EAC. Usually passes between cochlea and semicircular canals **(SCC)** sparing the VII and VIII nerves, but may disrupt ossicular chain
2. transverse fracture: perpendicular to EAC. Often passes through cochlea and may place stretch on geniculate ganglion, resulting in VIII and VII nerve deficits respectively

POSTTRAUMATIC FACIAL PALSY

Posttraumatic unilateral peripheral facial nerve palsy may be associated with petrous bone fractures as noted above.

Management

Management is often complicated by multiplicity of injuries (including head injury requiring endotracheal intubation) making it difficult to determine the time of onset of facial palsy. Guidelines:

1. regardless of time of onset:
   A. steroids (glucocorticoids) are often utilized (efficacy unproven)
   B. consultation with ENT physician is usually indicated

2. immediate onset of unilateral peripheral facial palsy: facial EMG (AKA electroneuronography[214] or **ENOG**) takes at least 72 hrs to become abnormal. These cases are often followed and are possible candidates for surgical VII nerve decompression if no improvement occurs with steroids (timing of surgery is controversial, but is usually not done emergently)
3. delayed onset of unilateral peripheral facial palsy: follow serial ENOGs, if continued nerve deterioration occurs while on steroids, and activity on ENOG drops to less than 10% of the contralateral side, surgical decompression may be considered (controversial, thought to improve recovery from ≈ 40% to ≈ 75% of cases)

CLIVAL FRACTURES[215]

3 categories (75% are longitudinal or transverse):

1. longitudinal: may be associated with injuries of vertebrobasilar vessels including:
   A. dissection or occlusion: may cause brain stem infarction
   B. traumatic aneurysms
2. transverse: may be associated with injuries to the anterior circulation
3. oblique

Clival fractures are highly lethal. May be associated with:

1. cranial nerve deficits: especially III through VI; bitemporal hemianopsia
2. CSF leak
3. diabetes insipidus

27.4.3. Craniofacial fractures

FRONTAL SINUS FRACTURES

Frontal sinus fractures account for 5-15% of facial fractures.

In the presence of a frontal sinus fracture, intracranial air (pneumocephalus) on CT even without a clinically evident CSF leak, must be presumed to be due to dural laceration (although it could also be due to a basal skull fracture, see *Pneumocephalus* below).

Anesthesia of the forehead may occur due to supratrochlear and/or supraorbital nerve involvement.

The risks of posterior wall fractures are not immediate, but may be delayed (some even by months or years) and include:

1. brain abscess
2. CSF leak with risk of meningitis
3. cyst or mucocele formation: injured frontal sinus mucosa has a higher predilection for mucocele formation than other sinuses[216]. Mucoceles may also develop as a result of frontonasal duct obstruction due to fracture or chronic inflammation. Mucoceles are prone to infection (mucopyocele) which can erode bone and expose dura with risk of infection

SURGICAL CONSIDERATIONS

Indications

Linear fractures of the anterior wall of the frontal sinus are treated expectantly.

Indications for exploration of posterior wall fractures is controversial[217]. Some argue that a few mm of displacement, or that CSF fistula that resolves may not require exploration. Others vehemently disagree.

Technique

In the presence of a traumatic forehead laceration, the frontal sinus may be exposed through judicious incorporation of the laceration in a forehead incision. Without such a laceration, either a bicoronal (souttar) skin incision or a butterfly incision (through the lower part of the eyebrows, crossing the midline near the glabella) is used.

Dealing with frontal sinus: ✖ Simple packing of the sinus (with bone wax, Gelfoam®, muscle or fat) increases the possibility of infection or mucocele formation.

The rear wall of the sinus is removed (so-called cranialization of the frontal sinus). The sinus is then exenterated (mucosa is stripped from sinus wall down to the nasofrontal duct, the mucosa is inverted over itself in the region of the duct and is packed down into the duct, temporalis muscle plugs are then packed into the frontonasal ducts[217]), then the bony wall of the sinus is drilled with a diamond burr to remove tiny remnants of mucosa found in the surface of bone that may proliferate and form a mucocele[216]. If there is any remnant of sinus, it may then be packed with abdominal fat that fills all corners of the cavity. Post-op

risks related to frontal sinus injury include: infection, mucocele formation and CSF leak.

In the presence of pneumocephalus, if no obvious dural laceration is found the dural undersurface of the frontal lobes should be checked for leaks. Extradural inspection and repair is rarely indicated; the act of lifting the dura off the floor of the frontal fossa in the region of the ethmoid sinuses often creates lacerations[218]. Intradural repair is accomplished using a graft (fascia lata is most desirable; periosteum is thinner but is often acceptable) which is held in place with sutures and must extend all the way back to the ridge of the sphenoid wing (fibrin glue may be a helpful adjunct).

A periosteal flap is placed across the floor of the frontal fossa to help isolate the dura from the frontal sinus and to prevent CSF fistula.

LEFORT FRACTURES

Complex fractures through inherently weak "cleavage planes" resulting in an unstable segment ("floating face"). Shown in *Figure 27-5* (usually occur as variants of this basic scheme).

- **LeFort I**: transverse AKA transmaxillary fracture. Fracture line crosses pterygoid plate and maxilla just above the apices of the upper teeth. May enter maxillary sinus(es)
- **LeFort II**: pyramidal. Fracture extends upward across inferior orbital rim and orbital floor to medial orbital wall, then across nasofrontal suture. Often from downward blow to the nasal area
- **LeFort III**: craniofacial dislocation. Involves zygomatic arches, zygomaticofrontal suture, nasofrontal suture, pterygoid plates, and orbital floors (separating maxilla from cranium). Requires significant force, therefore often associated with other injuries, including brain injuries

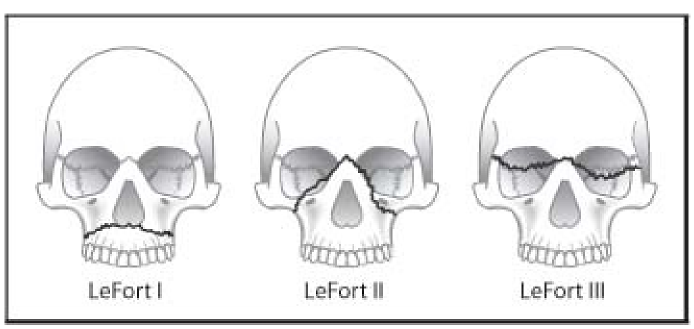


Figure 27-5 LeFort fractures

PNEUMOCEPHALUS

AKA (intra)cranial aerocele, AKA pneumatacele, is defined as the presence of intracranial gas. It is critical to distinguished this from **tension pneumocephalus** which is gas under pressure (*see below*). The gas may be located in any of the following compartments: epidural, subdural, subarachnoid, intraparenchymal, intraventricular.

Presentation: H/A in 38%, N/V, seizures, dizziness, and obtundation[219]. An intracranial succussion splash is a rare (occurring in ≈ 7%) but pathognomonic finding. Tension pneumocephalus may additionally cause signs and symptoms just as any mass (may cause focal deficit or increased ICP).

Etiologies of pneumocephalus:
Anything that can cause a CSF leak can produce associated pneumocephalus (*see page 301*).

1. skull defects
   - A. post neurosurgical procedure
     1. craniotomy: risk is higher when patient is operated in the sitting position[220]
     2. shunt insertion[221, 222]
     3. burr-hole drainage of chronic subdural hematoma[223, 224]: incidence is probably < 2.5%[224] although higher rates have been reported
   - B. posttraumatic
     1. fracture through air sinus: including basal skull fracture
     2. open fracture over convexity (usually with dural laceration)
   - C. congenital skull defects: including defect in tegmen tympani[225]
   - D. neoplasm (osteoma[226], epidermoid[227], pituitary tumor): usually caused by tumor erosion through floor of sella into sphenoid sinus
2. infection
   - A. with gas-producing organisms
   - B. mastoiditis
3. post invasive procedure:
   - A. lumbar puncture
   - B. ventriculostomy
   - C. spinal anesthesia[228]
4. spinal trauma (LP could be included here as well)
5. barotrauma[229]: e.g. with scuba diving (possibly through a defect in the

tegmen tympani)

6. may be potentiated by a CSF drainage device in the presence of a CSF leak[230]

Differential diagnosis (things that can mimic pneumocephalus):

Although intracranial low-density on CT may be associated with epidermoid, lipoma, or CSF, nothing is as intensely black as air. This can often be better appreciated on bone-windows than on soft-tissue windows.

Tension pneumocephalus

Intracranial gas can develop elevated pressure in the following settings:

1. when nitrous oxide anesthesia is not discontinued prior to closure of the dura[231] (see *nitrous oxide (N_2O)*, page 2)
2. "ball-valve" effect due to an opening to the intracranial compartment with soft tissue (e.g. brain) that may permit air to enter but prevent exit of air or CSF
3. when trapped room temperature air expands with warming to body temperature: a modest increase of only ≈ 4% results from this effect[232]
4. in the presence of continued production by gas-producing organisms

Diagnosis

Pneumocephalus is most easily diagnosed on CT[233] which can detect quantities of air as low as 0.5 ml. Air appears dark black (darker than CSF) and has a Hounsfield coefficient of –1000. One characteristic finding with bilateral pneumocephalus is the **Mt. Fuji sign** in which the two frontal poles appear peaked and are surrounded by and separated by air, resembling the silhouette of the twin peaks of Mt. Fuji[224] (*see Figure 27-6*). Intracranial gas may also be evident on plain skull x-rays.

Since simple pneumocephalus usually does not require treatment, it is critical to differentiate it from tension pneumocephalus, which may need to be evacuated if symptomatic. It may be difficult to distinguish the two; brain that has been compressed e.g. by a chronic subdural may not expand immediately post-op and the "gas gap" may mimic the appearance of gas under pressure.

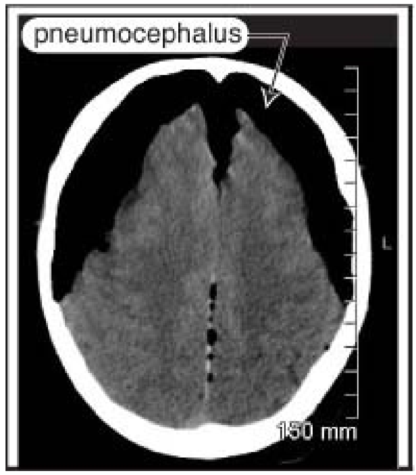


Figure 27-6 Mt. Fuji sign with bilateral pneumocephalus. Axial noncontrast CT scan

Treatment

When pneumocephalus is due to gas-producing organisms, treatment of the primary infection is initiated and the pneumocephalus is usually followed.

Treatment of non-infectious simple pneumocephalus depends on the whether or not the presence of a CSF leak is suspected. If there is no leak the gas will be resorbed with time, and if the mass effect is not severe it may simply be followed. If a CSF leak is suspected, management is as with any CSF fistula (see *CSF fistula (cranial)*, page 300).

Treatment of significant or symptomatic post-op pneumocephalus by breathing 100% O_2 via a nonrebreather mask increases the rate of resorption[234] (100% FiO_2 can be tolerated for 24-48 hours without serious pulmonary toxicity[235]).

Tension pneumocephalus producing significant symptoms must be evacuated. The urgency is similar to that of an intracranial hematoma. Dramatic and rapid improvement may occur with the release of gas under pressure. Options include placement of new twist drill or burr holes, or insertion of a spinal needle through a pre-existing burr hole (e.g. following a craniotomy).

27.4.4. Skull fractures in pediatric patients

This section deals with some special concerns of skull fractures in pediatrics. Also see *Child abuse*, page 918.

POSTTRAUMATIC LEPTOMENINGEAL CYSTS

AKA **growing skull fractures**. Posttraumatic leptomeningeal cysts **(PTLMC)** are distinct from arachnoid cysts (AKA leptomeningeal cysts, which are not posttraumatic). PTLMC consists of a fracture line that widens with time. Although usually asymptomatic, the cyst may cause mass effect with neurologic deficit. Traumatic aneurysm is another rare complication[236].

PTLMCs are very rare, occurring in 0.05-0.6% of skull fractures[237, 238]. Usually requires both a widely separated fracture AND a dural tear. Mean age at injury: < 1 year, over 90% occur before age 3 years[239] (formation may require the presence of a rapidly growing brain[240]) although rare adult cases have been described[241-243] (a total of 5 cases in the literature as of 1998243). Most often presents as scalp mass, although there are two reports of presentation with head pain alone[241]. PTLMC rarely occur > 6 mos out from the injury. Some children may develop a skull fracture that seems to grow during the initial few weeks, that is not accompanied by a subgaleal mass, and that heal spontaneously within several months; the term "pseudogrowing fracture" has been suggested for these[244].

X-ray appearance: widening of fracture and scalloping (or saucering) of edges.

TREATMENT

Treatment of true PTLMC is surgical, with dural closure mandatory. Since the dural defect is usually larger than the bony defect, it may be advantageous to perform a craniotomy around the fracture site, repair the dural defect, and replace the bone[242]. Pseudogrowing fractures should be followed with x-rays and operated only if expansion persists beyond several months or if a subgaleal mass is present.

SCREENING FOR DEVELOPMENT OF PTLMC

If early growth of a fracture line with no subgaleal mass is noted, repeat skull films in 1-2 months before operating (to rule-out pseudogrowing fracture). In young patients with separated skull fractures (the width of the initial fracture is rarely mentioned), consider obtaining follow-up skull film 6-12 mos post-trauma. However, since most PTLMCs are brought to medical attention when the palpable mass is noticed, routine follow-up x-rays may not be cost-effective.

27.5. Posttraumatic parenchymal injuries

For techniques of decompressive craniectomies, *see page 165*.

CEREBRAL EDEMA

Surgical decompression is occasionally an option (*see PRACTICE GUIDELINE 27-21*).

PRACTICE GUIDELINE 27-21 POSTTRAUMATIC CEREBRAL EDEMA
Indications and timing for surgery
Level III[245]: bifrontal decompressive craniectomy within 48 hrs of injury is a treatment option for patients with diffuse, medically refractory posttraumatic cerebral edema and associated IC-HTN

DIFFUSE INJURIES

Patients with severe diffuse injuries occasionally may be considered for decompressive craniectomy (*see PRACTICE GUIDELINE 27-22*).

PRACTICE GUIDELINE 27-22 DIFFUSE INJURIES
Indications for surgery
Level III[245]: decompressive craniectomy is an option for patients with refractory IC-HTN and diffuse parenchymal injury with clinical and radiographic evidence for impending transtentorial herniation

27.5.1. Hemorrhagic contusion

AKA traumatic intracerebral hemorrhage **(TICH)**. Often considered as high density areas on CT (some exclude areas < 1 cm diameter[246]). TICH usually produce much less mass effect than their apparent size. Most commonly occur in areas where sudden deceleration of the head causes the brain to impact on bony prominences (e.g. temporal, frontal and occipital poles) in coup or contrecoup

fashion.

TICH often enlarge and/or coalesce with time as seen on serial CTs. They also may appear in a delayed fashion (see *Delayed traumatic intracerebral hemorrhage (DTICH)* below). CT scans months later often show surprisingly minimal or no encephalomalacia.

Treatment

PRACTICE GUIDELINE 27-23 SURGICAL MANAGEMENT OF TICH

Level III[245]: Indications for surgery for TICH:

- surgical evacuation for:
  A. progressive neurological deterioration referable to the TICH, medically refractory IC-HTN, or signs of mass effect on CT
  B. or TICH volume > 50 cm^3
  C. or GCS = 6-8 with frontal or temporal TICH volume > 20 cm^3 with midline shift (MLS - *see page 909*) ≥ 5 mm and/or compressed basal cisterns on CT (*see page 909*)
- nonoperative management with intensive monitoring and serial imaging: may be used for TICH without neurologic compromise and no significant mass effect on CT and controlled ICP

DELAYED TRAUMATIC INTRACEREBRAL HEMORRHAGE (DTICH)

In patients with GCS ≤ 8, incidence is ≈ 10%[247, 248] (reported incidence varies with resolution of CT scanner[41], timing of scan, and definition). Most DTICH occur within 72 hrs of the trauma[248]. Some patients seem to be doing well and then present with an apoplectic event (although DTICH accounted only for 12% of patients who "talk and deteriorate"[249]).

Factors that contribute to formation of DTICH include local or systemic coagulopathy, hemorrhage into an area of necrotic brain softening, coalescence of extravasated microhematomas[250].

Treatment is the same as for TICH (*see above*).

Outcome for patients with DTICH described in the literature is generally poor, with a mortality ranging from 50-75%[250].

27.6. Epidural hematoma

Incidence of epidural hematoma **(EDH)**: 1% of head trauma admissions (which is ≈ 50% the incidence of acute subdurals). Ratio of male:female = 4:1. Usually occurs in young adults, and is rare before age 2 yrs or after age 60 (perhaps because the dura is more adherent to the inner table in these groups).

Dogma was that a temporoparietal skull fracture disrupts the middle meningeal artery as it exits its bony groove at the pterion, causing arterial bleeding that dissects the dura from the inner table. Alternatively, dissection of the dura from the inner table may occur first, followed by bleeding into the space thus created.

Source of bleeding: 85% = arterial bleeding (the middle meningeal artery is the most common source of middle fossa EDHs). Many of the remainder of cases are due to bleeding from middle meningeal vein or dural sinus.

70% occur laterally over the hemispheres with their epicenter at the pterion, the rest occur in the frontal, occipital, and posterior fossa (5-10% each).

Presentation with EDH

"Textbook" presentation (< 10%-27% have this classical presentation[68]):

- brief posttraumatic loss of consciousness **(LOC)**
- followed by a "**lucid interval**" for several hours
- then, obtundation, contralateral hemiparesis, ipsilateral pupillary dilatation

Deterioration usually occurs over a few hours, but may take days and rarely, weeks (longer intervals may be associated with venous bleeding).

Other presenting findings: H/A, vomiting, seizure (may be unilateral), hemi-hyperreflexia + unilateral Babinski sign, and elevated CSF pressure (LP is seldom used any longer). Bradycardia is usually a late finding. In peds, EDH should be suspected if there is a 10% drop in hematocrit after admission.

Contralateral hemiparesis is not uniformly seen, especially with EDH in locations other than laterally over the hemisphere. Shift of the brain stem away from the mass may produce compression of the opposite cerebral peduncle on tentorial notch which can produce *ipsilateral* hemiparesis (so called **Kernohan's phenomenon** or Kernohan's notch phenomenon)[251], a false localizing sign.

60% of patients with EDH have a dilated pupil, 85% of which are <u>ipsilateral</u>.

No initial loss of consciousness occurs in 60%. No lucid interval in 20%.

Beware: lucid interval may also be seen in other conditions (including subdural hematoma).

Differential diagnosis: Includes a posttraumatic disorder described by Denny-Brown consisting of a “lucid interval” followed by bradycardia, brief periods of restlessness and vomiting, without intracranial hypertension or mass. Children especially may have H/A, and may become drowsy and confused. Theory: a form of vagal syncope, but CT must be done to rule-out EDH.

Evaluation

Plain skull x-rays

No fracture is identified in 40% of EDH. In these cases the patient’s age was almost always < 30 yrs.

CT scan in EDH

“Classic” CT appearance occurs in 84% of cases: high density biconvex (lenticular) shape adjacent to the skull. In 11% the side against the skull is convex and that along the brain is straight, and in 5% it is crescent shaped (resembling subdural hematoma)[252]. An EDH may cross the falx (distinct from SDH which is limited to one side of the falx) but is usually limited by skull sutures. EDH usually has uniformly density, sharply defined edges on multiple cuts, high attenuation (undiluted blood), contiguous with inner table, usually confined to small segment of calvaria. Mass effect is frequent. Occasionally, an epidural may be isodense with brain and may not show up unless IV contrast is given[252].

Mortality with EDH

Overall: 20-55% (higher rates in older series). Optimal diagnosis and treatment within few hours results in 5-10% estimated mortality (12% in a recent CT era series[253]). Mortality without lucid interval double that with. Bilateral Babinski’s or decerebration pre-op → worse prognosis. Death is usually due to respiratory arrest from uncal herniation causing injury to the midbrain.

20% of patients with EDH on CT also have ASDH at autopsy or operation. Mortality with both lesions concurrently is higher, reported range: 25-90%.

Treatment of EDH

MEDICAL

CT may detect small EDHs and can be used to follow them. However, in most cases, EDH is a surgical condition (see *Surgical indications and timing (see PRACTICE GUIDELINE 27-24)* below).

Nonsurgical management may be attempted in the following:

Small (≤ 1 cm maximal thickness) subacute or chronic EDH[254], with minimal neurological signs/symptoms (e.g. slight lethargy, H/A) and no evidence of herniation. Although medical management of p-fossa EDHs has been reported, these are more dangerous and surgery is recommended.

In 50% of cases there will be a slight transient increase in size between days 5-16, and some patients required emergency craniotomy when signs of herniation occurred[255].

Management

Management includes: admit, observe (in monitored bed if possible). Optional: steroids for several days, then taper. Follow-up CT: in 1 wk if clinically stable. Repeat in 1-3 mos if patient becomes asymptomatic (to document resolution). Prompt surgery if signs of local mass effect, signs of herniation (increasing drowsiness, pupil changes, hemiparesis…) or cardiorespiratory abnormalities.

SURGICAL

Surgical indications and timing (*see PRACTICE GUIDELINE 27-24*)

EDH in pediatric patients is riskier than adults since there is less room for clot. Threshold for surgery in pediatrics should be very low.

PRACTICE GUIDELINE 27-24 SURGICAL MANAGEMENT OF EDH

Indications for surgery

Level III[256]:

- EDH volume > 30 cm^3 should be evacuated regardless of GCS
- EDH with the *all* of the following characteristics can be managed non-surgically with serial CT scans and close neurological observation in a neurosurgical center:
  - A. volume < 30 cm^3

B. *and* thickness < 15 mm
C. *and* with midline shift **(MLS)** < 5 mm (*see page 909*)
D. *and* GCS > 8
E. *and* no focal neurologic deficit

Timing of surgery

Level III[256]: it is strongly recommended that patients with an acute EDH and GCS < 9 and anisocoria undergo surgical evacuation ASAP

Booking the case - craniotomy for acute EDH/SDH

Also see defaults & disclaimers (*page v*).

1. position: (depends on location of bleed, usually supine)
2. blood: type & screen (for severe SDH: T & C 2 U PRBC)
3. post-op: ICU
4. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the skull to remove blood clot, stop any bleeding identified, possible placement of intracranial pressure monitor
   B. alternatives: nonsurgical management
   C. complications: (usual craniotomy complications - *see page v*) *plus* further bleeding which may cause problems (especially in patients taking blood thinners, antiplatelet drugs including aspirin, or those with coagulation abnormalities or previous bleeds) and may require further surgery, any permanent brain injury that has already occurred is not likely to recover, hydrocephalus

Surgical technical issues

Evacuation is performed in the O.R. unless the patient herniates in E/R. Objectives:

1. clot removal: lowers ICP and eliminates focal mass effect. Blood is usually thick coagulum, thus exposure must provide access to most of clot. Craniotomy permits more complete evacuation of hematoma than e.g. burr holes[256]
2. hemostasis: coagulate bleeding soft tissue (dural veins & arteries). Apply

bone wax to intradiploic bleeders (e.g. middle meningeal artery). Also requires large exposure
3. prevent reaccumulation: (some bleeding may recur, and dura is now detached from inner table) place dural tack-up sutures to edges of craniotomy and use central "tenting" suture

DELAYED EPIDURAL HEMATOMA (DEDH)

Definition: an EDH that is not present on the initial CT scan, but is found on subsequent CT. Comprise 9-10% of all EDHs in several series[257, 258].

Theoretical risk factors for DEDH include the following (NB: many of these risk factors may be incurred <u>after</u> the patient is admitted following a negative initial CT):

1. lowering ICP either medically (e.g. osmotic diuretics) and/or surgically (e.g. evacuating contralateral hematoma) which reduces tamponading effect
2. rapidly correcting shock (hemodynamic "surge" may cause DEDH)[259]
3. coagulopathies

DEDH have been reported in <u>mild</u> head injury (GCS > 12) infrequently[260]. Presence of a skull fracture has been identified as a common feature of DEDH[260].

Key to diagnosis: high index of suspicion. Avoid a false sense of security imparted by an initial "nonsurgical" CT. 6 of 7 patients in one series improved or remained unchanged neurologically despite enlarging EDH (most eventually deteriorate). 1 of 5 with an ICP monitor did not have a heralding increase in ICP. May develop once an intracranial lesion is surgically treated, as occurred in 5 of 7 patients within 24 hrs of evacuation of another EDH. 6 of 7 patients had known skull fractures in the region where the delayed EDH developed[258], but none of 3 had a skull fracture in another report[259].

POSTERIOR FOSSA EPIDURAL HEMATOMA

Comprise ≈ 5% of EDH[261, 262]. More common in 1st two decades of life. Although as many as 84% have occipital skull fractures, only ≈ 3% of children with occipital skull fractures develop p-fossa EDH. The source of bleeding is usually not found, but there is a high incidence of tears of the dural sinuses. Cerebellar signs are surprisingly lacking or subtle in most. For surgical indications, *see page 905*. Overall mortality is ≈ 26% (mortality was higher in

patients with an associated intracranial lesion).

27.7. Subdural hematoma

27.7.1. Acute subdural hematoma

The magnitude of impact damage (as opposed to secondary damage, *see page 854*) is usually much higher in acute subdural hematoma **(ASDH)** than in epidural hematomas, which generally makes this lesion much more lethal. There is often associated underlying brain injury, which may be less common with EDH. Symptoms may be due to compression of the underlying brain with midline shift, in addition to parenchymal brain injury and possibly cerebral edema[263, 264].

Two common causes of traumatic ASDH:

1. accumulation around parenchymal laceration (usually frontal or temporal lobe). There is usually severe underlying primary brain injury. Often no "lucid interval". Focal signs usually occur later and are less prominent than with EDH
2. surface or bridging vessel torn from cerebral acceleration-deceleration during violent head motion. With this etiology, primary brain damage may be less severe, a lucid interval may occur with later rapid deterioration

ASDH may also occur in patients receiving anticoagulation therapy[265, 266], usually with but sometimes without a history of trauma (the trauma may be minor). Receiving anticoagulation therapy increases the risk of ASDH 7-fold in males and 26-fold in females[265].

CT scan in ASDH

Crescentic mass of increased attenuation adjacent to inner table. Edema is often present. Usually over convexity, but may also be interhemispheric, along tentorium, or in p-fossa. Membrane formation begins by about 4 days after injury[267]. Changes with time on CT (*see Table 27-25*):isodense after ≈ 2 wks, only clues may be obliteration of sulci and lateralizing shift, the latter may be absent if bilateral. Subsequently becomes hypodense to brain (see *Chronic subdural hematoma*, page 899).

Differences from EDH: SDH is more diffuse, less uniform, usually concave

over brain surface, often less dense (from mixing with CSF), and bridging subdural veins (from brain surface to the skull) may be seen.

Table 27-25 ASDH density changes on CT with time

Category	Time frame	Density on CT
acute	1 to 3 days	hyperdense
subacute	4 days to 2 or 3 wks	≈ isodense
chronic	usually > 3 wks and < 3-4 mos	hypodense (approaching density of CSF)
	after about 1-2 months	may become lenticular shaped (similar to epidural hematoma) with density > CSF, < fresh blood

Treatment

Level III surgical indications are shown in *PRACTICE GUIDELINE 27-25*. Other factors that should be considered:

1. presence of anticoagulants or platelet inhibitors: patients in good neurologic condition may be better served by reversing these agents prior to operating (to increase the safety of surgery)
2. location of hematoma: in general, a SDH high over the convexity is less threatening than a temporal/parietal SDH of the same volume that also has MLS
3. patient's baseline level of function, DNR status…
4. while the guidelines suggest evacuating SDH < 10 mm thick in some circumstances, clots that are smaller than this may simply be an epiphenomenon

PRACTICE GUIDELINE 27-25 SURGICAL MANAGEMENT OF ASDH

Indications for surgery

Level III[268]:

- ASDH with thickness > 10 mm or midline shift **(MLS)** > 5 mm (on CT) should be evacuated regardless of GCS
- ASDH with thickness < 10 mm* and MLS < 5 mm should undergo surgical evacuation if:
  A. GCS drops by ≥ 2 points from injury to admission
  B. *and/or* the pupils are asymmetric or fixed and dilated

C. *and/or* ICP is > 20 mm Hg

• monitor ICP in all patients with ASDH and GCS < 9

Timing of surgery

Level III[268]: ASDH meeting surgical criteria should be evacuated ASAP[†]

Surgical methods

Level III[268]: ASDH meeting the above criteria for surgery should be evacuated via craniotomy[‡] with or without bone flap removal and duraplasty

* see text regarding the evacuation of ASDH < 10 mm thick

† for issues regarding timing of surgery, see text

‡ a large craniotomy flap is often required to evacuate the thick coagulum and to gain access to possible bleeding sites.

Booking the case - acute subdural hematoma

As for acute epidural hematoma (*see page 895*).

Technical considerations

The actual bleeding site is often not identified at the time of surgery. One may start with a small linear dural opening to effect clot removal and enlarge it as needed and only if brain swelling seems controllable.

Morbidity and mortality with ASDH

Mortality

Range: 50-90% (a significant percentage of this mortality is from the underlying brain injury, and not the ASDH itself).

Traditionally thought to be higher in aged patients (60%). 90-100% in patients on anticoagulants[266].

"Four hour rule"

Based on a 1981 series of 82 patients with ASDH[269], it had been widely held

that:

1. patients operated within 4 hrs of injury had 30% mortality, compared to 90% mortality if surgery was delayed > 4 hrs
2. functional survival (Glasgow Outcome Scale ≥ 4, see *Table 34-3*, page 1183) rate of 65% could be achieved with surgery within 4 hrs
3. other factors related to outcome in this series include:
   A. post-op ICP: 79% of patients with functional recovery had post-op ICPs that didn't exceed 20 mm Hg, whereas only 30% of patients who died had ICP < 20 mm Hg
   B. initial neuro exam
   C. age was not a factor (ASDH tend to occur in older patients than EDH)

However, the magnitude of the importance of rapid surgical treatment is still controversial. A study of 101 patients with ASDH found overall mortality of 66%, and functional recovery of 19%[270]. Postoperative seizures occurred in 9%, and did not correlate with outcome. The following was determined:

1. delay to surgery: delays > 4 hours increased mortality from 59% to 69% and decreased functional survival (Glasgow Outcome Scale ≥ 4, *see page 1183*) from 26% to 16%. These differences suggested a trend but were not statistically significant
2. the following variables were identified as strongly influencing outcome:
   A. mechanism of injury: the worst outcome was with motorcycle accidents, with 100% mortality in unhelmeted patients, 33% in helmeted
   B. age: correlated with outcome only > 65 yrs age, with 82% mortality and 5% functional survival in this group (other series had similar results[271])
   C. neurologic condition on admission: the ratio of mortality to functional survival rate related to the admission Glasgow Coma Scale **(GCS)** is shown in *Table 27-26*
   D. postoperative ICP: patients with peak ICPs < 20 mm Hg had 40% mortality, and no patient with ICP > 45 had a functional survival

Of all the above factors, only the time to surgery and postoperative ICP can be directly influenced by the treating neurosurgeon.

Table 27-26 Outcome as related to admission GCS

GCS	Mortality	Functional survival

3	90%	5%
4	76%	10%
5	62%	18%
6 & 7	51%	44%

INTERHEMISPHERIC SUBDURAL HEMATOMA

Subdural hematoma along the falx between the two cerebral hemispheres (older term: interhemispheric scissure).

May occur in children[272], possibly associated with child abuse[273].

In adults, a consequence of head trauma in 79-91%, ruptured aneurysm[274] in ≈ 12%, surgery in the vicinity of the corpus callosum, and rarely spontaneously[275].

Incidence is unknown. Spontaneous cases should be investigated for possible underlying aneurysm. Occasionally may be bilateral, sometimes may be delayed (*see below*)

Most often are asymptomatic, or may present with the so-called “falx syndrome” - paresis or focal seizures contralateral to the hematoma. Other presentations: gait ataxia, dementia, language disturbance, oculomotor palsies.

Treatment

Controversial. Small asymptomatic cases may be managed expectantly. Surgery should be considered for progressive neurological deterioration. Approached through a parasagittal craniotomy. ✖ Surgery for these lesions can be treacherous - there is risk of venous infarction and often you find you are dealing with a superior sagittal sinus injury.

Outcome

Reported mortality: 25-42%. Mortality is higher in the presence of altered levels of consciousness. Mortality rate may actually be lower (24%) than with all-comers[275]. This is significantly lower than SDH in other sites (*see above*).

DELAYED ACUTE SUBDURAL HEMATOMA (DASDH)

DASDHs have received less attention than delayed epidural or intraparenchymal hematomas. Incidence is ≈ 0.5% of operatively treated ASDHs[250].

Definition: ASDH not present on an initial CT (or MRI) that shows up on a

subsequent study. Indications for treatment are the same as for ASDH. Neurologically stable patients with a small DASDH and medically controllable ICP are managed expectantly.

INFANTILE ACUTE SUBDURAL HEMATOMA

Infantile acute subdural hematoma **(IASDH)** is often considered as a special case of SDH. Roughly defined as an acute SDH in an infant due to minor head trauma without initial loss of consciousness or cerebral contusion[276], possibly due to rupture of a bridging vein. The most common trauma is a fall backwards from sitting or standing. The infants will often cry immediately and then (usually within minutes to 1 hour) develop a generalized seizure. Patients are usually < 2 yrs old (most are 6-12 mos, the age when they first begin to pull themselves up or walk)[277].

These clots are rarely pure blood, and are often mixed with fluid. 75% are bilateral or have contralateral subdural fluid collections. It is speculated that IASDH may represent acute bleeding into a preexisting fluid collection[277].

Skull fractures are rare. In one series, retinal and preretinal hemorrhages were seen in all 26 patients[276].

Treatment

Treatment is guided by clinical condition and size of hematoma. Minimally symptomatic cases (vomiting, irritability, no altered level of consciousness and no motor disturbance) with liquefied hematoma may be treated with percutaneous subdural tap, which may be repeated several times as needed. Chronically persistent cases may require a subduroperitoneal shunt.

More symptomatic cases with high density clot on CT require craniotomy. A subdural membrane similar to those seen in adult chronic SDH is not unusual[277]. Caution: these patients are at risk of developing intraoperative hypovolemic shock.

Outcome

8% morbidity and mortality rate in one series[276]. Much better prognosis than ASDH of all ages probably because of the absence of cerebral contusion in IASDH.

27.7.2. Chronic subdural hematoma

Chronic subdural hematomas **(CSDH)** generally occur in the elderly, with the average age being ≈ 63 yrs (exception: subdural collections of infancy, *see page 904*). Head trauma is identified in < 50% (sometimes rather trivial trauma). Other risk factors: alcohol abuse, seizures, CSF shunts, coagulopathies (including therapeutic anticoagulation[266]), and patients at risk for falls (e.g. with hemiplegia from previous CVA). CSDHs are bilateral in ≈ 20-25% of cases[278, 279].

Hematoma thickness tends to be larger in older patients due to a decrease in brain weight and increase in subdural space with age[280].

Classically CSDHs contains dark "motor oil" fluid which does not clot[281]. When the subdural fluid is clear (CSF), the collection is termed a subdural hygroma (*see page 903*).

Pathophysiology

Many CSDH probably start out as acute subdurals. Blood within the subdural space evokes an inflammatory response. Within days, fibroblasts invade the clot, and form neomembranes on the inner (cortical) and outer (dural) surface. This is followed by ingrowth of neocapillaries, enzymatic fibrinolysis, and liquefaction of blood clot. Fibrin degradation products are reincoporated into new clots and inhibit hemostasis. The course of CSDH is determined by the balance of plasma effusion and/or rebleeding from the neomembranes on the one hand and reabsorption of fluid on the other[282, 283].

Presentation

Patients may present with minor symptoms of headache, confusion, language difficulties (e.g. word-finding difficulties or speech arrest, usually with dominant hemisphere lesions), or TIA-like symptoms (*see page 1201*). Or, they may develop varying degrees of coma, hemiplegia, or seizures (focal, or less often generalized). Often, the diagnosis may be unexpected prior to imaging. Specialized clinical grading systems have been published, but are not widely used.

TREATMENT

1. seizure prophylaxis: used by some. Fully load with phenytoin (17 mg/kg slow IV, see *phenytoin (PHT) (Dilantin®)*, page 409) and follow with 100 mg slow IV q 8 hrs. It may be safe to discontinue after a week or so if

there are no seizure. If late seizure occurs with or without prior use of AEDs, longer-term therapy is required. Some feel that the incidence of side effects from AEDs approximates the incidence of seizures and therefore they do not recommend prophylactic AEDs
2. coagulopathies (and iatrogenic anticoagulation) should be reversed
3. surgical evacuation of hematoma indicated for:
   A. symptomatic lesions: including focal deficit, mental status changes…
   B. or subdurals with maximum thickness greater than ≈ 1 cm

SURGICAL CONSIDERATIONS

Booking the case - craniotomy: for chronic subdural

Also see defaults & disclaimers (*page v*).
1. position: (usually supine), horseshoe headrest
2. post-op: ICU
3. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the skull to remove blood clot, stop any bleeding identified, placement a drainage tube to allow further fluid to drain after surgery for a day or so
   B. alternatives: nonsurgical management
   C. complications: (usual craniotomy complications - *see page v*) *plus* further bleeding which may cause problems (especially in patients taking blood thinners, antiplatelet drugs including aspirin, or those with coagulation abnormalities or previous bleeds) and may require further surgery, hydrocephalus

Surgical options

There is not uniform agreement on the best method to treat CSDHs. For details of techniques (burr holes, whether or not to use subdural drain…) *see below*.
1. placing two burr holes, and irrigating through and through with tepid saline until the fluid runs clear
2. single “large” burr hole with irrigation and aspiration: *see below*
3. single burr hole drainage with placement of a subdural drain, maintained

for 24-48 hrs (removed when output becomes negligible)

4. twist drill craniostomy: *see below* (note that small "twist drill" drainage without subdural drain has higher recurrence rate than e.g. burr holes)
5. formal craniotomy with excision of subdural membrane (may be necessary in cases which persistently recur after above procedures, possibly due to seepage from the subdural membrane). Still a safe and valid technique[284]. No attempt should be made to remove the deep membrane adherent to the surface of brain

Techniques that promote continued drainage after the immediate procedure and that may thus reduce residual fluid and prevent reaccumulation:

1. use of a subdural drain: (*see below*)
2. using a generous burr hole under the temporalis muscle: (*see below*)
3. bed-rest restriction with the head of the bed flat (1 pillow is permitted) with mild overhydration for 24-48 hours post-op (or if a drain is used, until 24-48 hours after it is removed). May promote expansion of the brain and expulsion of residual subdural fluid. Allowing patients to sit up to 30-40° immediately post-op was associated with higher radiographic recurrence rate (2.3% for those kept flat, vs. 19% for those who sat up) but usually did not require reoperation[285]
4. some advocate continuous lumbar subarachnoid infusion when the brain fails to expand, however there are possible complications[223]

TWIST DRILL CRANIOSTOMY FOR CHRONIC SUBDURALS

This method is thought to decompress the brain more slowly and avoids the presumed rapid pressure shifts that occurs following other methods, which may be associated with complications such as intraparenchymal (intracerebral) hemorrhage. May even be performed at the bedside under local anesthesia.

A 0.5 cm incision is made in the scalp in the rostral portion of the hematoma, and then a twist drill hole is placed at a 45° angle to the skull, aimed in the direction of the longitudinal axis of the collection. If the drill does not penetrate the dura, this is done with an 18 Ga. spinal needle. A ventricular catheter is inserted into the subdural space, and is drained to a standard ventriculostomy drainage bag maintained 20 cm below the level of the craniostomy site[286-288] (see *Subdural drain* below). The patient is kept flat in bed (*see above*). Serial CTs assess the adequacy of drainage. The catheter is removed when at least ≈ 20% of the collection is drained and when the patient shows signs of improvement, which occurs within a range of 1-7 days (mean of 2.1 days). Some

include a low pressure shunt valve in the system to prevent reflux of fluid or air.

BURR HOLES FOR CHRONIC SUBDURAL HEMATOMAS

To prevent recurrence, the use of small burr holes (without a subdural drain) is not recommended. A generous (> 2.5 cm diameter - it is recommended that one actually measure this) subtemporal craniectomy should be performed, and bipolar coagulation is used to shrink the edges of the dura and subdural membrane back to the full width of the bony opening (do not try to separate these two layers as this may promote bleeding). This allows continued drainage of fluid into the temporalis muscle. A piece of Gelfoam® may be placed over the opening to help prevent fresh blood from oozing into the opening.

SUBDURAL DRAIN

Use of a subdural drain is associated with a decrease in need for repeat surgery from 19% to 10%[289]. If a subdural drain is used, a closed drainage system is recommended. Difficulties may occur with ventriculostomy catheters because the holes are small and are restricted to the tip region (so-designed to keep choroid plexus from plugging the catheter when inserted into the ventricles when used as intended as a CSF shunt), especially with thick "oily" fluid (on the positive side, slow drainage may be desirable). The drainage bag is maintained ≈ 50-80 cm below the level of the head[288, 290]. An alternative is a small Jackson-Pratt® drain using "thumb-print" indentation of the suction bulb which provides good drainage with a self-contained one-way valve (however, there may be a risk of excessive negative pressure with overcompression of the bulb).

Post-op, the patient is kept flat (*see above*). Prophylactic antibiotics may be given until ≈ 24-48 hrs following removal of the drain, at which time the HOB is gradually elevated. CT scan prior to removal of the drain (or shortly after removal) may be helpful to establish a baseline for later comparison in the event of deterioration.

There is a case report of administration of urokinase through a subdural drain to treat reaccumulation of clot following evacuation[291].

OUTCOME

There is clinical improvement when the subdural pressure is reduced to close to zero, which usually occurs after ≈ 20% of the collection is removed[288].

Patients who have high subdural fluid pressure tend to have more rapid brain expansion and clinical improvement than patients with low pressures[290].

Residual subdural fluid collections after treatment are common, but clinical

improvement does not require complete resolution of the fluid collection on CT. CTs showed persistent fluid in 78% of cases on post-op day 10, and in 15% after 40 days[290], and may take up to 6 months for complete resolution. Recommendation: do not treat persistent fluid collections evident on CT (especially before ≈ 20 days post-op) unless it increases in size on CT or if the patient shows no recovery or deteriorates.

76% of 114 patients were successfully treated with a single drainage procedure using a twist drill craniostomy with subdural ventricular catheter, and 90% with one or two procedures[286]. These statistics are slightly better than twist drill craniostomy with aspiration alone (i.e. no drain).

Complications of surgical treatment

Although these collections often appear innocuous, severe complications may occur, and include:

1. seizures (including intractable status epilepticus)
2. intracerebral hemorrhage **(ICH)**: occurs in 0.7-5%[292]. Very devastating in this setting: one third of these patients die and one third are severely disabled
3. failure of the brain to re-expand and/or reaccumulation of the subdural fluid
4. tension pneumocephalus
5. subdural empyema: may also occur with untreated subdurals[293]

In 60% of patients ≥ age 75 yrs (and in no patients < 75 yrs), rapid decompression is associated with **hyperemia** in the cortex immediately beneath the hematoma, which may be related to the complications of ICH or seizures[292]. All complications are more common in elderly or debilitated patients.

Overall mortality with surgical treatment for CSDH is 0-8%[292]. In a series of 104 patients treated mostly with craniostomy[294], mortality was ≈ 4%, all of which occurred in patients > 60 yrs old and were due to accompanying disease. Another large personal series reported 0.5% mortality[295]. Worsening of neurologic status following drainage occurs in ≈ 4%[294].

27.7.3. Spontaneous subdural hematoma

Occasionally patients with no identifiable trauma will present with severe H/A with or without associated findings (nausea, seizures, lethargy, focal

findings including possible ipsilateral hemiparesis[296]…) and CT or MRI discloses a subdural hematoma that may be acute, subacute or chronic in appearance. The onset of symptoms is often sudden[296].

Risk factors

Risk factors identified in a review of 21 cases in the literature[297] include:

1. hypertension: present in 7 cases
2. vascular abnormalities: arteriovenous malformation **(AVM)**, aneurysm[298]
3. neoplasm
4. infection: including meningitis, tuberculosis
5. substance abuse: alcoholism, cocaine[299]
6. hypovitaminosis: especially vitamin C deficiency[300]
7. coagulopathies, including:
   A. iatrogenic (anticoagulation e.g. with warfarin)
   B. Ginkgo biloba **(GB)** extract: EGb761 and LI1379. Contains ginkgolides (especially Type B) which are inhibitors of platelet activating factor (PAF) at high concentrations[301], also cause vasodilation and decreased blood viscosity. There have been case reports showing temporal relationship of hemorrhage to intake of GB[302], especially at higher doses over long periods of time. However, no consistent alteration was demonstrable in 29 measurable coagulation/clotting variables after 7 days[303] (bleeding time was mildly prolonged in some case reports[302, 304]). Some individuals may possibly be more susceptible to the supplement, and there may be as-yet uncharacterized interactions with other entities (such as alcohol, aspirin…) but studies so far have been unrevealing[305]
   C. factor XIII deficiency (protransglutaminase)[306, 307]. In peds: history may include report of bleeding from umbilical cord at birth. Check factor XIII levels as coagulation parameters may be normal or only slightly elevated
8. seemingly innocuous insults (e.g. bending over) or injuries resulting in no direct trauma to the head (e.g. whiplash injuries)
9. intracranial hypotension: spontaneous, after epidural anesthesia, lumbar puncture, or VP shunt[308, 309]

Etiology

The bleeding site was determined in 14 of the 21 cases, and was arterial in each, typically involving a cortical branch of the MCA in the area of the sylvian fissure[297] where there is a large number of branches to a wide cortical area.

Possible mechanisms for arterial rupture in idiopathic acute subdural hematoma **(ASDH)** include tears occur secondary to sudden head movements or trivial head trauma of the following[310, 311]:

1. small artery at perpendicular branch point off a cortical artery
2. small artery connecting the dura and cortex
3. adhesions between cortical artery and dura

Treatment

As for traumatic SDH. If symptomatic and/or > ≈ 1 cm thick, surgical evacuation is the treatment of choice. For subacute to chronic subdurals, burr-hole evacuation is usually adequate (*see above*). For acute SDH, a craniotomy is usually required, and should expose the sylvian fissure to identify bleeding point(s). Microsurgical repair of arterial wall has been described[311].

27.7.4. Traumatic subdural hygroma

From the Greek *hygros* meaning wet. AKA traumatic subdural effusion, AKA hydroma. Excess fluid in the subdural space (may be clear, blood tinged, or xanthochromic and under variable pressure) is almost always associated with head trauma, especially alcohol-related falls or assaults[312]. Skull fractures were found in 39% of cases. Distinct from chronic subdural hematoma, which is usually associated with underlying cerebral contusion, and usually contains darker clots or brownish fluid ("motor oil" fluid), and may show membrane formation adjacent to inner surface of dura (hygromas lack membranes).

"Simple hygroma" refers to a hygroma without significant accompanying conditions. "Complex hygroma" refers to hygromas with associated significant subdural hematoma, epidural hematoma, or intracerebral hemorrhage.

On CT, the density of the fluid is similar to that of CSF.

Pathogenesis

Mechanism of formation of hygroma is probably a tear in the arachnoid membrane with resultant CSF leakage into the subdural compartment. Hygroma fluid contains pre-albumin, which is also found in CSF but not in subdural hematomas. The most likely locations of arachnoid tears are in the sylvian

fissure or the chiasmatic cistern. Another possible mechanism is post-meningitis effusion (especially influenza meningitis).

May be under high pressure. May increase in size (possibly due to a flap-valve mechanism) and exert mass effect, with the possibility of significant morbidity. Cerebral atrophy was present in 19% of patients with simple hygromas.

Table 27-27 Major clinical features of traumatic subdural hygromas[312]

Type of hygroma	Simple	Complex	Total
number of patients	66	14	80
spontaneous eye opening	74%	57%	71%
disorientation or stupor	65%	57%	64%
mental status change without focal signs	52%	50%	51%
neurological plateau with deficit or delayed deterioration	42%	7%	36%
seizures (usually generalized)	36%	43%	38%
hemiparesis	32%	21%	30%
neck stiffness	26%	14%	24%
anisocoria (maintained light reflex)	15%	7%	14%
headache	14%	14%	14%
alert (no mental status change)	8%	0%	6%
hemiplegia	6%	14%	8%
comatose (responsive to pain only)	3%	43%	10%

Presentation

Table 27-27 shows clinical findings of subdural hygromas. Many present without focal findings. Complex hygromas usually present more acutely and require more urgent treatment.

Treatment

Asymptomatic hygromas do not require treatment. Recurrence following simple burr-hole drainage is common. Many surgeons maintain a subdural drain for 24-48 hrs post-op. Recurrent cases may require either a craniotomy to locate the site of CSF leak (may be very difficult), or a subdural-peritoneal shunt may be placed.

Outcome

Outcome may be more related to accompanying injuries than to the hygroma itself.

5 of 9 patients with complex hygromas and subdural hematoma died. For simple hygromas, morbidity was 20% (12% for decreased mental status without focal findings, 32% if hemiparesis/plegia was present).

27.7.5. Extraaxial fluid collections in children

Differential diagnosis

1. benign subdural collection in infants (*see below*)
2. chronic symptomatic extraaxial fluid collections or effusions (*see below*)
3. cerebral atrophy: should not contain xanthochromic fluid with elevated protein
4. "external hydrocephalus": ventricles often enlarged, fluid is CSF (*see page 307*)
5. normal variant of enlarged subarachnoid spaces and interhemispheric fissure
6. acute subdural hematoma: high density (fresh blood) on CT (occasionally these will appear as low density collections in children with low hematocrits). Will usually be unilateral (the others above are usually bilateral). These lesions may occur as birth injuries, and typically present with seizures, pallor, tense fontanelle, poor respirations, hypotension, and retinal hemorrhages
7. "craniocerebral disproportion" (head too large for the brain)[313]: extracerebral spaces enlarged up to 1.5 cm in thickness and filled with CSF-like fluid (possibly CSF), ventricles at upper limits of normal, deep sulci, widened interhemispheric fissure, normal intracranial pressure. Patients are developmentally normal. May be the same as benign extra-axial fluid of infancy (*see below*). Making this diagnosis with certainty is difficult in first few months of life

BENIGN SUBDURAL COLLECTIONS OF INFANCY

Benign subdural collections (or effusions) of infancy[314, 315], are perhaps better characterized by the term **benign extra-axial fluid collections of infancy**, since it is difficult to distinguish whether they are subdural or subarachnoid[316]. They appear on CT as peripheral hypodensities over the frontal lobes in infants. Imaging may also show dilatation of the interhemispheric fissure, cortical sulci[317], and sylvian fissure. Ventricles are usually normal or slightly enlarged,

with no evidence of transependymal absorption. Brain size is normal. Transillumination is increased over both frontal regions. The fluid is usually clear yellow (xanthochromic) with high protein content. The etiology of these is unclear, some cases may be due to perinatal trauma. They are more common in term infants than preemies. Must be differentiated from external hydrocephalus (*see page 307*).

Presentation: Mean age of presentation is ≈ 4 months[316].

May show: signs of elevated intracranial pressure (tense or large fontanelle, accelerated head growth crossing percentile curves), developmental delay usually as a result of poor head control due to the large size (developmental delay without macrocrania runs counter to the concept of "benign"[316]), frontal bossing, jitteriness. The poor head control may lead to positional flattening. Other symptoms, such as seizures (possibly focal) are indicative of symptomatic collections (*see below*). Large collections in the *absence* of macrocrania are more suggestive of cerebral atrophy.

Treatment: Most cases gradually resolve spontaneously, often within 8-9 months. A single subdural tap (*see page 201*) for diagnostic purposes (to differentiate from cortical atrophy and to rule out infection) may be done, and may accelerate the rate of disappearance. Repeat physical exams with OFC measurements should be done at ≈ 3-6 month intervals. Head growth usually parallels or approaches normal curves by ≈ 1-2 yrs age, and by 30-36 months orbital-frontal head circumference **(OFC)** approaches normal percentiles for height and weight. They usually catch up developmentally as OFCs normalize.

SYMPTOMATIC CHRONIC EXTRAAXIAL FLUID COLLECTIONS IN CHILDREN

Variously classified as hematomas (chronic subdural hematoma), effusions, or hygromas, with differing definitions associated with each. Since the appearance on imaging and the treatment is similar, Litofsky et al. proposed that they all be classified as extraaxial fluid collections[318]. The difference between these lesions and "benign" subdural effusions (*see above*) may simply be the degree of clinical manifestation.

Etiologies

The following etiologies were listed in a series of 103 cases[318]:

1. 36% were thought to be the result of trauma (22 were victims of child

abuse)
2. 22% followed bacterial meningitis (post-infectious)
3. 19 occurred after placement or revision of a shunt (*see* *page 327*)
4. no cause could be identified in 17 patients

Other causes include[313]:
1. tumors: extracerebral or intracerebral
2. post-asphyxia with hypoxic brain damage and cerebral atrophy
3. defects of hemostasis: vitamin K deficiency…

Signs and symptoms

Symptoms include: seizure (26%), large head (22%), vomiting (20%), irritability (13%), lethargy (13%), headache (older children), poor feeding, respiratory arrest…

Signs include: full fontanelle (30%), macrocrania (25%), fever (17%), lethargy (13%), hemiparesis (12%), retinal hemorrhages, coma, papilledema, developmental delay…

Evaluation

CT/MRI usually shows ventricular compression and obliteration of the cerebral sulci, unlike with benign subdural collections. The "cortical vein sign" (*see* *page 308*) helps distinguish this from external hydrocephalus.

Treatment

Options include:
1. observation: follow-up with serial OFC measurements, ultrasound and CT/MRI
2. serial percutaneous subdural taps (*see* *page 201*): some patients require as many as 16 taps[319]. Some series show good results and others show low success rate[320, 321]
3. burr hole drainage: may include long-term external drainage. Simple burr hole drainage may not be effective with severe craniocephalic disproportion as the brain will not expand to obliterate the extra-axial space
4. subdural-peritoneal shunt: unilateral shunt is usually adequate even for bilateral effusions[318, 321, 322] (no study is required to demonstrate

communication between the 2 sides[318, 323]). An extremely low pressure system should be utilized. The general practice is to remove the shunt after 2-3 months of drainage (once the collections are obliterated) to reduce the risk of associated mineralization of the dura and arachnoid and possible risk of seizures (these shunts are easily removed at this time, but may be more difficult to remove at a later date)[324]

Other recommendations:

At least one percutaneous tap should be performed to rule-out infection.

Many authors recommend observation for the patient with no symptoms or with only enlarging head and developmental delay.

27.8. Traumatic posterior fossa mass lesions

Less than 3% of head injuries involve the posterior fossa[325]. Epidural hematomas constitute the majority of these (*see page 896*). Other entities (subdural hematoma, intraparenchymal hematoma[326]) comprise the small remainder. *PRACTICE GUIDELINE 27-26* shows surgical management recommendations. Any of these can cause hydrocephalus[325].

Most parenchymal hemorrhages managed nonsurgically were < 3 cm diameter.

PRACTICE GUIDELINE 27-26 SURGICAL MANAGEMENT OF TRAUMATIC POSTERIOR FOSSA MASS LESIONS

Indications for surgery

Level III[327]:

- symptomatic posterior fossa mass lesions or those with mass effect on CT* should be surgically removed
- asymptomatic lesions without mass effect on CT may be managed with close observation and serial imaging

Timing of surgery

Level III[327]: p-fossa mass lesions meeting surgical criteria should be evacuated ASAP due to the potential for rapid deterioration

Surgical methods

Level III[327]: suboccipital craniectomy is the recommended procedure

* mass effect on CT: defined as dislocation, compression or obliteration of the 4th ventricle; compression or loss of basal cisterns (see page 909), or the presence of obstructive hydrocephalus

27.9. Posttraumatic hydrocephalus

Hydrocephalus was found in 40% of 61 patients with severe head injury (GCS = 3-8) and in 27% of 34 patients with moderate head injury (GCS = 9-13)[328]. Hydrocephalus developed by 4 weeks after injury in 58% and by 2 months in 70%[328]. There was no statistically significant relationship between posttraumatic hydrocephalus and age, the presence of SAH, or type of lesion (focal or diffuse). Posttraumatic hydrocephalus was associated with worse outcome[328].

Differentiating true hydrocephalus from hydrocephalus ex vacuo

Delayed ventricular enlargement months to years after TBI may instead be due to atrophy (hydrocephalus ex vacuo) secondary to diffuse axonal injury, and may not represent true hydrocephalus. It may not be possible to accurately differentiate these two conditions, and the decision to shunt may therefore be difficult (similar to the dilemma in patients with NPH vs. atrophy).

Factors favoring hydrocephalus, for which shunt should be considered:

1. elevated pressure on 1 or more LPs
2. papilledema on funduscopic exam
3. symptoms of headache/pressure
4. findings of "transependymal absorption" on CT or T2WI MRI (*see page 310*)
5. ± patient's whose neurologic recovery seems worse than expected
6. provocative tests have been recommended[329] (*see page 332*)

Patients with enlarged ventricles who are asymptomatic and are doing well following their head injury should be managed expectantly.

HYDROCEPHALUS AFTER TRAUMATIC SUBARACHNOID HEMORRHAGE

Incidence of clinically symptomatic hydrocephalus within 3 months of traumatic subarachnoid hemorrhage **(tSAH)** is ≈ 12%[330]. In this series of 301 tSAH patients, multivariate analysis showed the risk of developing hydrocephalus increased with age, intraventricular hemorrhage, blood thickness ≥ 5 mm, and diffuse distribution of blood (vs. focal distribution). There was no correlation with gender, admission GCS score, basal location of tSAH, or use of decompressive craniectomy[330]. NB: this is potentially confusing, univariate analysis shows the risk of hydrocephalus increases with increasing severity of TBI.

27.10. Aspects of general care in severe TBI

27.10.1. Airway management

See page 861 for indications for, and use of antibiotics with, intubation.

PRACTICE GUIDELINE 27-27 TIMING OF TRACHEOSTOMY
Level II[52]: early tracheostomy reduces the number of days of mechanical ventilation but does not affect mortality or incidence of pneumonia

PRACTICE GUIDELINE 27-28 TIMING OF EXTUBATION
Level III[52]: early extubation for patients meeting extubation criteria does not increase the risk of pneumonia

27.10.2. Deep-vein thrombosis (DVT) prophylaxis

Also, *see page 42* for further details about thromboembolism in neurosurgical patients. The risk of developing DVT is ≈ 20% in untreated severe TBI[331]. *PRACTICE GUIDELINE 27-29* delineates some aspects of DVT prophylaxis.

PRACTICE GUIDELINE 27-29 DVT PROPHYLAXIS IN SEVERE TBI

Level III[332]:

- unless contraindicated, graduated compression stockings or intermittent compression boots are recommended until patients are ambulatory
- low molecular weight heparin **(LMWH)** (*see* *page 39*) or low-dose unfractionated heparin in conjunction with mechanical measures lowers the DVT risk, but a trend suggests they increase the risk of expansion of intracranial hemorrhage*

* there is insufficient evidence: to support use of one pharmacologic agent over another, or to define the optimal dose or timing of agents[332]

27.10.3. Nutrition in the head-injured patient

SUMMARY OF RECOMMENDATIONS (*SEE TEXT* FOR DETAILS)

PRACTICE GUIDELINE 27-30 NUTRITION

Level II[333]: full caloric replacement should be attained by post-trauma day 7

Σ

1. by post-trauma day 7, replace the following (enterally or parenterally):
   A. non-paralyzed patients: 140% of predicted basal energy expenditure **(BEE)**
   B. paralyzed patients: 100% of predicted BEE
2. provide ≥ 15% of calories as protein
3. nutritional replacement should begin within 72 hrs of head injury in order to achieve goal #1 by day 7
4. the enteral route is preferred (IV hyperalimentation is preferred if higher nitrogen intake is desired or if there is decreased gastric emptying)

RATIONALE

CALORIC REQUIREMENTS

Rested comatose patients with isolated head injury have a metabolic expenditure that is 140% of normal for that patient (range: 120-250%)[50, 334-336]. Paralysis with muscle blocker or barbiturate coma reduced this excess expenditure in most patients to ≈ 100-120% of normal, but some remained elevated by 20-30%[337]. Energy requirements rise during the first 2 weeks after

injury, but it is not known for how long this elevation persists. Mortality is reduced in patients who receive full caloric replacement by day 7 after trauma[338]. Since it generally takes 2-3 days to get nutritional replacement up to speed whether the enteral or parenteral route is utilized[50], it is recommended that nutritional supplementation begin within 72 hrs of head injury.

Enteral vs. IV hyperalimentation: Caloric replacement that can be achieved is similar between enteral or parenteral routes[339]. The enteral route is preferred because of reduced risk of hyperglycemia, infection and cost[340]. IV hyperalimentation may be utilized if higher nitrogen intake is desired or if there is decreased gastric emptying. No significant difference in serum albumin, weight loss, nitrogen balance, or final outcome was found between enteral and parenteral nutrition[339].

Estimates of basal energy expenditure **(BEE)** can be obtained from the **Harris-Benedict equation**[341], shown in *Eq 27-4* through *Eq 27-6*, where W is weight in kg, H is height in cm, and A is age in years.

$$\text{Males: BEE} = 66.47 + 13.75 \times W + 5.0 \times H - 6.76 \times A \qquad \textbf{Eq 27-4}$$

$$\text{Females: BEE} = 65.51 + 9.56 \times W + 1.85 \times H - 4.68 \times A \qquad \textbf{Eq 27-5}$$

$$\text{Infants: BEE} = 22.1 + 31.05 \times W + 1.16 \times H \qquad \textbf{Eq 27-6}$$

Enteral nutrition

Isotonic solutions (such as Isocal® or Osmolyte®) should be used at full strength starting at 30 ml/hr. Check gastric residuals q 4 hrs and hold feedings if residuals exceed ≈ 125 ml in an adult. Increase the rate by ≈ 15-25 ml/hr every 12-24 hrs as tolerated until the desired rate is achieved[342]. Dilution is not recommended (may slow gastric emptying), but if it is desired, dilute with normal saline to reduce free water intake.

Cautions:

NG tube feeding may interfere with absorption of phenytoin (see *phenytoin (PHT) (Dilantin®)*, page 409). Reduced gastric emptying may be seen following head-injury[343] (NB: some may have temporarily *elevated* emptying) as well as in pentobarbital coma, patients may need IV hyperalimentation until the enteric route is usable. Others have described better tolerance of enteral feedings using jejunal administration[344].

Nitrogen balance

As an estimate, for each gram of N excreted (mostly in the urine, however, some is also lost in the feces), 6.25 gm of protein have been catabolized. It is recommended that at least 15% of calories be supplied as protein. The percent of calories consumed **(PCC)** derived from protein can be calculated from *Eq 27-7*, where N is nitrogen in grams, and BEE is the basal energy expenditure[334] (*see Eq 27-4* through *Eq 27-6*).

$$\text{PCC (from protein)} = \frac{\text{N (gm N)} \times \frac{6.25\ \text{gm protein}}{\text{gm N}} \times \frac{4.0\ \text{kcal}}{\text{gm protein}}}{\text{BEE}} \times 100 \qquad \textbf{Eq 27-7}$$

Thus, to supply PCC (protein) = 15% once the BEE is known, use *Eq 27-8*. Some enteral formulations include Magnacal® (PCC = 14%) and Trauma-Cal® (PCC = 22%).

$$\text{N (gm N)} = 0.006 \times \text{BEE} \qquad \textbf{Eq 27-8}$$

27.11. Outcome from head trauma

27.11.1. Age

In general, the degree of recovery from closed head injury is better in infants and young children than in adults. In adults, decerebrate posturing or flaccidity with loss of pupillary or oculovestibular reflex is associated with a poor outcome in most cases, these findings are not as ominous in pediatrics.

27.11.2. Outcome prognosticators

The frequency of poor outcome from closed head injury is increased with persistent ICP > 20 mm Hg after hyperventilation, increasing age, impaired or absent pupillary light response or eye movement, hypotension (SBP < 90), hypercarbia, hypoxemia, or anemia[79]. This is probably due at least in part to the fact that some of these are markers for significant injury to other body systems. One of the most important predictors for poor outcome is the presence of a mass

lesion requiring surgical removal[345]. High ICP during the first 24 hrs is also a poor prognosticator.

Midline shift **(MLS)**

The presence of MLS correlates with a worse outcome. For the purpose of standardizing measurements in trauma, MLS is defined at the level of the foramen of Monro[346] as shown in *Figure 27-7*, and is calculated using *Eq 27-9*,

$$\text{midline shift (MLS)} = \frac{\text{BPD}}{2} - \text{SP} \qquad \textbf{Eq 27-9}$$

where the midline is found by dividing the biparietal diameter **(BPD)** (the width of intracranial compartment at this location) by 2, and subtracting **SP** (the distance from the inner table to the septum pellucidum on the side of the shift). Measurements may be inaccurate if the vertical axis of the patient's head is not parallel to the long axis of the CT scanner. Midline shift may be associated with altered levels of consciousness (*see page 280*).

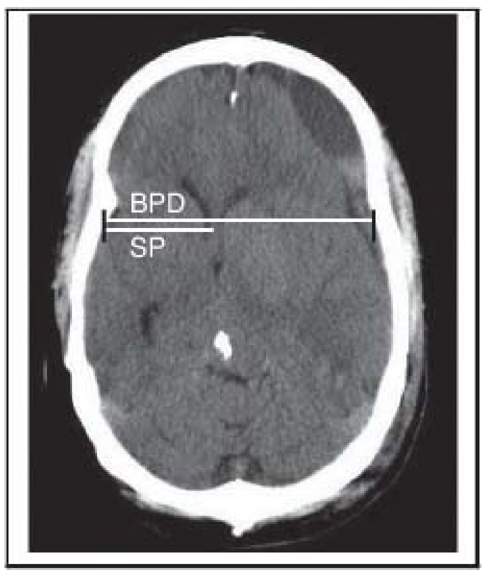


Figure 27-7 Measurement of midline shift (CT of a patient with subdural hematoma)

Obliteration of basal cisterns on CT

The status of the basal cisterns[A] **(BCs)** is evaluated on axial CT scan at the level of the midbrain (*see Figure 27-8*) where they are divided into 3 limbs[346] (1 posterior limb = quadrigeminal cistern, 2 lateral limbs = posterior portion of the ambient cisterns). Possible findings:

A. “basal cisterns” in the trauma literature are a subset of the perimesencephalic cisterns, *see page 1085*

1. open: all 3 limbs open
2. partially closed: 1 or 2 limbs obliterated
3. completely closed: 3 limbs obliterated

Compression or absence of the BCs carries a threefold risk of increased ICP, and the status of the BCs correlates with outcome[346].

In a study of 218 patients with GCS ≤ 8, the BCs were classified on initial CT (within 48 hrs of admission) as: absent, compressed, normal, or not visualized (quality of CT too poor to tell)[347]. The relationship of the BCs to outcome is shown in *Table 27-28*. 18 patients had a shift of brain structures > 15 mm associated with absent BCs, all of them died. The status of the BCs were more important within each GOS score than across scores. Also, see *Table 27-7*, page 854 for more information on CT.

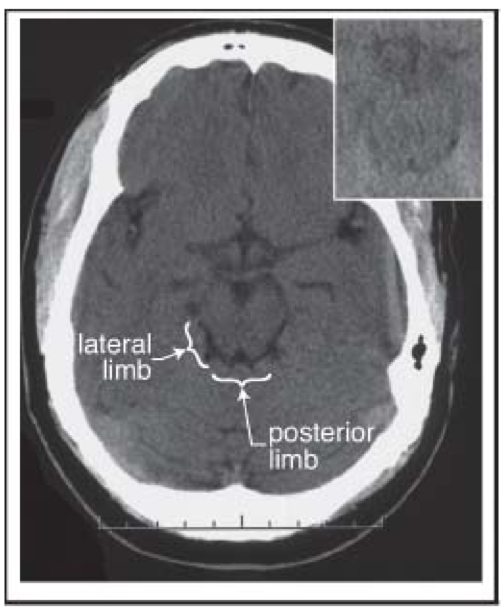


Figure 27-8 Basal cisterns CT demonstrating open basal cisterns (inset: example of ≈ complete obliteration of BCs)

Apolipoprotein E (apoE) e4 allele

The presence of this genotype portends a worse prognosis following traumatic brain injury[348]. Furthermore, the incidence of severe brain injury in

individuals with the apoE-4 allele greatly exceeds the rate of the allele in the general population[349]. This allele is also a risk factor for Alzheimer's disease (*see below*) as well as for chronic traumatic encephalopathy (*see page 912*).

Table 27-28 Correlation of GOS* with basal cisterns

Basal cisterns	--- OUTCOME* ---				
	Mortality	Vegeta-tive	Severe disability	Moderate disability	Good
	(GOS 1)	(GOS 2)	(GOS 3)	(GOS 4)	(GOS 5)
normal	22%	6%	16%	21%	35%
compressed	39%	7%	18%	17%	19%
absent	77%	2%	6%	4%	11%
not-visualized	68%	0%	11%	9%	12%

* GOS = Glasgow outcome scale, see *Table 34-3*, page 1183

27.11.3. Late complications from traumatic brain injury

Long term complications include:

1. posttraumatic seizures: (*see page 398*)
2. communicating hydrocephalus: incidence ≈ 3.9% of severe head injuries
3. posttraumatic syndrome (or postconcussive syndrome): *see below*
4. hypogonadotropic hypogonadism[350]: also *see page 863*
5. chronic traumatic encephalopathy (*see page 911*)
6. Alzheimer's disease **(AD)**: head injury (especially if severe) promotes the deposition of amyloid proteins, especially in individuals possessing the apolipoprotein E (apoE) ε4 allele[349], which may be related to the development of AD[351-353]

POSTCONCUSSIVE SYNDROME

Variously defined collection of symptoms (*see below*) that is usually considered as a possible sequelae to minor head trauma (although some of these features can be seen following more serious head trauma). Loss of consciousness is not a prerequisite.

Controversy exists over the relative contribution of actual organic dysfunction vs. psychological factors (including conversion reaction, secondary gain which may be for attention, financial reward, drug seeking…). Furthermore,

the presence of some of these symptoms can undoubtedly lead to the development of others (e.g headache can cause difficulty concentrating and thus poor job performance and thence depression).

A paradox has been noted by clinicians that the complaints following minor head injury seem out of proportion when considered in the context of the frequency of complaints after serious head injury. It has also been noted that patients with early post-traumatic complaints generally improve with time, whereas the late development of symptoms is often associated with a more protracted and fulminant course.

Symptoms commonly considered part of this syndrome include the following (with headache, dizziness and memory difficulties being the most frequent):

1. somatic
   A. headache
   B. dizziness or light-headedness
   C. visual disturbances: blurring is a common complaint
   D. anosmia
   E. hearing difficulties: tinnitus, reduced auditory acuity
   F. balance difficulties
2. cognitive
   A. difficulty concentrating
   B. dementia: more common with multiple brain injuries than with a single concussion (see *Chronic traumatic encephalopathy*, page 911)
      1. loss of intellectual ability
      2. memory problems: usually impairs short-term memory
   C. impaired judgement
3. psychosocial
   A. emotional difficulties: including depression, mood swings (emotional lability), euphoria/giddiness, easy irritability, lack of motivation, abulia
   B. personality changes
   C. loss of libido
   D. disruption of sleep/wake cycles, insomnia
   E. easy fatigability
   F. intolerance to light (photophobia) and/or loud (or even moderate) noise
   G. increased rate of job loss and divorce (may be related to any of above)

Virtually any symptom can be ascribed to the condition. Other symptoms that may be described by patients which are generally not included in the

definition:

1. fainting (vaso-vagal episodes): may need to rule out posttraumatic seizures, as well as other causes of syncope
2. altered sense of taste
3. dystonia[354]

Treatment

Treatment for symptoms attributed to this syndrome tends to be supportive. Often times these patients obtain treatment from primary care physicians, neurologists, physiatrists, and/or psychiatrists/psychologists. Neurosurgical involvement in the continuing care for these patients is usually at the discretion of the individual physician based on his or her practice patterns. Recovery follows a highly variable course.

Some symptoms may need to be evaluated for possible correctable late complications (seizures, hydrocephalus, CSF leak…). Alves and Jane[355] perform a head CT, MRI, BAER and neuropsychological battery if symptoms after minor head injury persist > 3 months. An EEG may be appropriate in cases where there is a question of seizures. If all studies are negative, "the authors tell the patient (and the lawyer) that there is no objective evidence for disease and that psychiatric evaluation is warranted." Non-correctable abnormalities on these studies prompt reassurance that significant symptoms should subside by 1 year, and that no specific treatment, other than psychological counselling, is helpful.

CHRONIC TRAUMATIC ENCEPHALOPATHY

Often described in retired boxers, chronic traumatic encephalopathy **(CTE)** encompasses a spectrum of symptoms that range from mild to a severe form AKA **dementia pugilistica**[356], or punch drunk syndrome. Symptoms involve motor, cognitive and psychiatric systems. CTE is distinct from post-traumatic dementia (which may follow a single closed head injury) or from post-traumatic Alzheimer's syndrome. Although generally accepted, not all authorities agree that repeated concussions have any long-term sequelae[357].

There are some similarities with Alzheimer's disease **(AD)**, including the presence of neurofibrillary tangles having similar microscopic characteristics and the development of amyloid angiopathy with the attendant risk of intracerebral hemorrhage[358]. EEG changes occur in one-third to one-half of professional boxers (diffuse slowing or low-voltage records).

Table 27-29 CTE of boxing*

Motor	Cognitive	Psychiatric
Early (≈ 57%)		
dysarthria tremors mild incoordination especially non-dominant hand	decreased complex attention	emotional lability euphoria/hypomania irritability, suspiciousness ease of aggression & talkativeness
Middle (≈ 17%)		
parkinsonism increased dysarthria, tremors, and incoordination	slowed mental speed mild deficits in memory, attention & executive ability	magnified personality decreased spontaneity paranoid, jealous inappropriate violent outbursts
Late (< 3%)		
pyramidal signs prominent parkinsonism prominent dysarthria, tremors & ataxia	prominent slowness of thought/speech amnesia attention deficits executive dysfunction	cheerful/silly decreased insight paranoid, psychotic disinhibited, violent possible Klüver-Bucy

* in professional boxers with ≥ 20 bouts

Clinical: Clinical features of CTE are shown in *Table 27-29*[356] and include:

1. cognitive: mental slowing and memory deficits (dementia)
2. personality changes: explosive behavior, morbid jealousy, pathological intoxication with alcohol, and paranoia
3. motor: cerebellar dysfunction, symptoms of Parkinson's disease, pyramidal tract dysfunction

Grading scales have been devised to rank patients as having probable, possible, and improbable CTE.

The chronic brain injury scale **(CBIS)** assesses involvement of motor, cognitive, and psychological axes as shown in *Table 27-30*.

Risk factors for dementia pugilistica in boxing[356]:

1. risk increases with length of boxing career, especially > 10 yrs
2. age at retirement: risk goes up after age 28 yrs
3. number of bouts: especially ≥ 20 (more important than the number of knock-outs)
4. boxing style: increased risk among poorer performers, those known as sluggers rather than "scientific" boxers, those known to be hard to knock

out or known to take a punch and keep going
5. age at examination: long latency causes increased prevalence with age
6. and possibly, the number of head blows
7. risk increases in patients with the apolipoprotein E (apo E) ε4 allele (as in Alzheimer's disease) as shown in *Table 27-31*
8. professional boxers (more risk than amateurs)

Table 27-30 Chronic brain injury scale

Grade involvement of each of the following axes separately: • motor • cognitive • psychological	Scoring for each axis: 0 = none 1 = mild 2 = moderate 3 = severe
Sum total points	**Severity**
0	normal
1 - 2	mild
3 - 4	moderate
> 4	severe

Neuro-imaging: The most common finding is cerebral atrophy. A cavum septum pellucidum **(CSP)** is observed in 13% of boxers[359]. CSP in this setting probably represents an acquired condition[360] and correlates with cerebral atrophy.

Table 27-31 Odds ratio for developing Alzheimer's disease

Head injury	Apo E ε 4 allele	Odds ratio
–	–	1
–	+	2
+	–	1
+	+	10

Neuropathology includes:
1. cerebral and cerebellar atrophy
2. neurofibrillary degeneration of cortical and subcortical areas
3. deposition of ß-amyloid protein
   A. forming diffuse amyloid plaques
   B. in a subset of CTE patients this involves the vessel walls giving rise to cerebral amyloid angiopathy

27.12. Gunshot wounds to the head

Gunshot wounds to the head **(GSWH)** account for the majority of penetrating brain injuries, and comprise ≈ 35% of deaths from brain injury in persons < 45 yrs old. GSWH are the most lethal type of head injury, ≈ two thirds die at the scene, and GSWH ultimately are the proximal cause of death in > 90% of victims[361].

PRIMARY INJURY

Primary injury from GSWH results from a number of factors including:

1. injury to soft tissue
   - A. direct scalp and/or facial injuries
   - B. soft tissue and bacteria may be dragged intracranially, the devitalized tissue may also then support growth of the bacteria
   - C. pressure waves of gas combustion may cause injury if the weapon is close
2. comminuted fracture of bone: may injure subjacent vascular and/or cortical tissue (depressed skull fracture). May act as secondary missiles
3. cerebral injuries from missile
   - A. direct injury to brain tissue in path of bullet, exacerbated by
     1. fragmentation of bullet
     2. ricochet off bone
     3. deviations of the bullet from a straight path as it travels: tumbling (forward rotation - pitch), yaw (rotation about vertical axis), rotation (spin), nutation
     4. deformation of bullet at impact: e.g. mushrooming
   - B. injury to tissue by shock waves, cavitation
4. coup + contrecoup injury from missile impact on head (may cause injuries distant from bullet path)

Because of the complexities of ballistics (some of which are described above) there is often more damage even though the bullet slows (losing kinetic energy).

Extent of primary injury is related to <u>impact velocity</u>:

- <u>impact</u> velocity > 100 m/s: causes explosive intracranial injury that is uniformly fatal (NB: impact velocity is less than muzzle velocity)

- non-bullet missiles (e.g. grenade fragments) are considered low velocity
- low muzzle velocity bullets (≈ < 250 m/s): as with most handguns. Tissue injury is caused primarily by laceration and maceration along a path slightly wider than missile diameter
- high muzzle velocity bullets (≈ 600-750 m/s): from military weapons and hunting rifles. Causes additional damage by shock waves and temporary cavitation (tissue pushed away from the missile causes a conical cavity of injury that may exceed bullet diameter many-fold, and causes low-pressure region which may draw surface debris into the wound)

SECONDARY INJURY

Cerebral edema occurs similar to closed head injury. ICP may rise rapidly within minutes (higher ICPs result from higher impact velocities). Cardiac output may also fall initially. Together, ↑ ICP and ↓ MAP adversely effect cerebral perfusion pressure.

Other common complicating factors include: DIC, intracranial hemorrhage from lacerated blood vessels.

LATE COMPLICATIONS

Late complications include:

1. cerebral abscess: migration of bullet may be a tip-off (*see below*). Usually associated with retained contaminated material (bullet, bone, skin…) but may also result from persistent communication with nasal sinuses
2. traumatic aneurysm[362]
3. seizures
4. fragment migration
   A. migration of a bullet: often indicates abscess[363] or, less commonly, a hematoma cavity. May also migrate within the ventricles
   B. intraventricular fragments may migrate and cause obstructive hydrocephalus[364]
5. lead toxicity: more of an issue with bullet in disc space (*see page 998*)

EVALUATION

Exam should describe visible entrance and exit wounds. In through-and-through missile wounds of the skull, the entrance wound is typically smaller than the exit wound due to bullet mushrooming. Entrance wounds may be especially small with direct contact of the muzzle to the head. At surgery or autopsy, the

entrance wound will typically show bevelling of the inner table, whereas exit wounds have a beveled outer table.

GRADING SYSTEMS

The Glasgow Coma Scale is still the most widely used system and allows better comparison between series than specialized scales for GSWHs. See *Outcome* below.

MANAGEMENT

INITIAL STABILIZATION

GENERAL MEASURES

1. CPR as required; endotracheal intubation if stuporous or airway compromised
2. additional injuries (e.g. chest wounds) identified and treated appropriately
3. usual precautions taken for spine injury
4. fluids as needed to replace estimated blood loss which may be variable: care to avoid excessive hydration (to minimize cerebral edema)
5. pressors to support MAP during and after fluid resuscitation

TREATMENT OF THE INJURY

Neurological assessment as rapidly as possible and as thoroughly as time permits.

Decision by experienced neurosurgeon regarding the ultimate treatment of the patient will determine appropriate steps to be taken. Patients with little CNS function (in the absence of shock) are unlikely to benefit from craniotomy. Supportive measures are indicated in most cases (for possibility of organ donation, opportunity for family to adjust to situation, and requirements for observation period to determine actual brain death).

In patients considered for further treatment, rapid deterioration at any point with signs of herniation requires immediate surgical intervention. As time permits, the following should be undertaken:

- initial steps
  A. control bleeding from scalp and associated wounds (hemostats on scalp vessels)
  B. shave scalp to identify entrance/exit sites, and to save time in the O.R.

- radiographic evaluation
  - A. AP and lateral skull films to localize metal and bone fragments, and to help identify entrance/exit sites (omit if time not available)
  - B. non-contrast CT scan of the brain: identifies bullet track, intracranial hematomas, intraparenchymal location of bone and metal
  - C. angiography is occasionally indicated (*see below*)
- medical treatment (similar to closed head injury)
  - A. assume ICP is elevated:
    1. elevate HOB 30-45° with head midline (avoids kinking jugular veins)
    2. **mannitol** (1 gm/kg bolus) as blood pressure tolerates
    3. **hyperventilate** to $PaCO_2$ = **30-35** mm Hg if indications are met (see *Indications for hyperventilation (HPV)*, page 881)
    4. steroids: (unproven efficacy) 10 mg dexamethasone IVP
  - B. prophylaxis against GI ulcers: H_2 antagonist (e.g. ranitidine 50 mg IVPB q 8 hrs), NG tube to suction
  - C. begin phenytoin **(PHT)** loading: effective in controlling acute seizures, incidence of late seizures are not reduced once PHT is stopped
  - D. antibiotics: generally used although no controlled study demonstrates efficacy in preventing meningitis or abscess. Most organisms are sensitive to penicillinase resistant agents, e.g. nafcillin, recommended for ≈ 5 days
  - E. tetanus toxoid administration

Angiography in GSWH

Rarely performed emergently. When done, usually performed on ≈ day 2-3.

Indications[365]:

1. unexpected delayed hemorrhage
2. a trajectory that would likely involve named vessels in a salvageable patient
3. large intraparenchymal hemorrhages in a salvageable patient

SURGICAL TREATMENT

Indications for surgery are controversial. Patients with minimal neurologic function, e.g. fixed pupils, decorticate or decerebrate posturing… (when not in

shock and with good oxygenation) should not be operated upon, because the chance of meaningful recovery is close to zero. Patients with less severe injuries should be considered for urgent operation.

Goals of surgery

1. debridement of devitalized tissue: less tissue is injured in civilian GSWH, but elevated ICP post-op may imply more vigorous debridement was needed, especially of non-eloquent brain (e.g. temporal tips)
2. evacuation of hematomas: subdural, intraparenchymal…
3. removal of accessible bone fragments[A]
4. retrieval of bullet fragment[A] for forensic purposes (note: everyone who handles the fragments may be subpoenaed to testify as to the "chain of evidence"). Large intact fragments should be sought as they tend to migrate

A. risk of infection and seizures due to retained bullet fragments is not high in civilian GSWH, therefore only accessible fragments should be sought and removed

5. obtaining hemostasis
6. watertight dural closure (usually requires graft)
7. separation of intracranial compartment from air sinuses traversed by bullet
8. identification of entry and exit wounds for forensic purposes (see *Evaluation* above)

Surgical technique

Some key points of surgical technique[366] (p 2098-104:

- positioning and draping should make both entry and exit wounds accessible
- devitalized tissue around the entry & exit wounds should be excised
- fractured bone should be excised by a circumferential craniectomy (craniotomy may be used in some civilian GSWH, the entry site within the craniotomy should be rongeured or drilled back to clean bone)
- air sinuses that are traversed should have the mucosa exenterated, and are then packed with muscle, and covered with a graft (e.g. periosteum or fascia lata) to separate them from intracranial compartment

• the dura is opened in a stellate fashion
• pulped brain is removed from within using suction and bipolar in an enlarging cone until healthy tissue is encountered (further injury to deep midline structures should be avoided, here, stay within bullet tract)
• contralateral fragments with no exit wound should only be removed if accessible
• intraventricular fragments can present significant risk. Ventriculoscopy (if available) may be well suited for removing these
• dural closure should be watertight; grafts of pericranium, temporalis fascia, or fascia lata grafts may be used; avoid dura substitutes
• cranioplasty should be delayed 6-12 months to reduce risk of infection
• a post-op CSF fistula that persists > 2 weeks should be repaired

ICP MONITORING

ICP is often elevated after surgical debridement[367] and monitoring may be warranted.

OUTCOME

Prognostic factors

1. level of consciousness is the most important prognostic factor: ≈ 94% of patients who are comatose with inappropriate or absent response to noxious stimulus on admission die, and half the survivors are severely disabled[368]
2. path of the bullet. Especially poor prognosis is associated with:
   A. bullets that cross the midline
   B. bullets that pass through the geographic center of the brain
   C. bullets that enter or traverse the ventricles
   D. the more lobes traversed by the bullet
3. hematomas seen on CT are poor prognostic findings
4. suicide attempts are more likely to be fatal

27.13. Non-missile penetrating trauma

This section deals with penetrating injuries to the brain (and to some extent to the spinal cord) excluding missile injuries (i.e. gunshot wounds - *see page 912*). Includes trauma from: knives, arrows, lawn darts… Injury to neural tissue tends to be more limited than with missiles because many of the associated injurious aspects of the missile are absent (*see page 912*).

Arrow injuries

As a result of the lower velocity (e.g. 58 m/s) compared to firearms and the sharp tip, injury is usually limited to tissue directly incised by the arrowhead[369].

Cases with foreign body still embedded

In penetrating trauma, it is usually not appropriate to remove any protruding part of the foreign body until the patient is in the operating room, unless it cannot be avoided. If possible, it is helpful to have another identical object for comparison in planning extrication of the embedded object[370]. To minimize extending the trauma to the CNS, the protruding object should be stabilized in some way during transportation and evaluation. Intraoperatively, devices such as the Greenberg retractor may be used to stabilize the object during preparation and the initial approach.

Indications for pre-op angiography

1. object passes in region of large named artery
2. object passes near dural sinuses
3. visible evidence of arterial bleeding: angiography is not appropriate if hemorrhage cannot be controlled

Surgical techniques

It is impossible to give details to cover every situation. Some guidelines:

1. empiric antibiotic coverage is appropriate (see *Meningitis post craniospinal trauma,* page 343). Take cultures from the wound and the foreign body to guide later antibiotic therapy
2. optimal control can usually be gained by performing a craniotomy up to and if possible around the object, such that removing the bone flap will not disturb the object. The last remnants of bone may then be removed with a rongeur

3. if at all possible open the dura before removing the object, since removal with the dura closed does not allow adequate control of any bleeding from the brain
4. removal of the object ideally should follow the entry trajectory if possible
5. although gunshot wounds are not sterile as once thought, they are probably less contaminated than penetrating wounds. One should debride any easily accessible impacted bone and other extracranial tissue and material along the track

Post-op care

1. a course of antibiotics are usually appropriate since infection is common
2. consider a post-op arteriogram to rule-out traumatic aneurysm

27.14. High altitude cerebral edema

Acute high-altitude sickness **(AHAS)** is a systemic disorder that affects individuals usually within 6-48 hrs after ascent to high altitudes. **Acute mountain sickness (AMS)** is the most common form of AHAS, with symptoms of nausea, headache, anorexia, dyspnea, insomnia and fatigue[371] and is often assessed using the Lake Louise system[372]. The incidence is ≈ 25% at 7,000 feet, and ≈ 50% at 15,000 feet. Other symptoms of AHAS include edema of feet and hands, and pulmonary edema (HAPE = high altitude pulmonary edema). Ocular findings include retinal hemorrhages[373], nerve fiber layer infarction, papilledema and vitreous hemorrhage[374]. Cerebral edema (**HACE** = high altitude cerebral edema), usually associated with pulmonary edema, may occur in severe cases of AHAS. Symptoms of HACE include: severe headache, mental dysfunction (hallucinations, inappropriate behavior, reduced mental status), and neurologic abnormalities (ataxia, paralysis, cerebellar findings).

The unproven "tight-fit" hypothesis postulated that individuals with less compliant CSF systems (smaller ventricles and CSF spaces) were more vulnerable to AMS[375]. A small study of 10 volunteers[376] analyzing CT scans before ascent and symptoms showed a trend that supports the hypothesis.

Prevention: gradual ascent, 2-4 day acclimatization at intermediate altitudes (especially to include sleeping at these levels), avoidance of alcohol or hypnotics.

Treatment of cerebral edema: immediate descent and oxygen (6-12 L/min by NC or facemask) are recommended. Dexamethasone 8 mg PO or IV followed by 4 mg q 6 hrs may help temporize.

27.15. Pediatric head injury

75% of children hospitalized for trauma have a head injury. Although most pediatric head injuries are mild and involve only evaluation or brief hospital stays, CNS injuries are the most common cause of pediatric traumatic death[377]. The overall mortality for all pediatric head injuries requiring hospitalization has been reported between 10-13%[378], whereas the mortality associated with severe pediatric head injury presenting with decerebrate posturing has been reported as high as 71%[379].

Differences between adult and pediatric head injury:

1. epidemiology:
   A. children often have milder injuries than adults
   B. lower chance of a surgical lesion in a comatose child[380]
2. types of injury: injuries peculiar to pediatrics
   A. birth injuries: skull fractures, cephalhematoma (*see below*), subdural or epidural hematomas, brachial plexus injuries (*see page 802*)
   B. perambulator/walker injuries
   C. child abuse (*see below*): shaken baby syndrome…
   D. injuries from skateboarding, scooters…
   E. lawn darts
   F. cephalhematoma: *see below*
   G. leptomeningeal cysts, AKA "growing skull fractures": *see page 892*
3. response to injury
   A. responses to head injury of older adolescent are very similar to adults
   B. "malignant cerebral edema": acute onset of severe cerebral swelling (probably due to hyperemia[17, 381]) following some head injuries, especially in young children (may not be as common as previously thought[382])
   C. posttraumatic seizures: more likely to occur within the 1st 24 hrs in children than in adults[383] (*see page 398*)

Imaging studies

PRACTICE GUIDELINE 27-31 IMAGING IN MINOR PEDIATRIC HEAD INJURY*

Recommendations†[384]: CT scan for children with neurologic or cognitive dysfunction, or suspicion of a depressed or basilar skull fracture
Recommendations†[384]: when a CT scan is not done in a child ≤ 1 year age meeting the above criteria (e.g. because of sedation concerns), a skull film may be considered

* Definitions: minor head injury: GCS ≥ 13; pediatrics = ages 1 month - 17 years of age. Excludes: suspicion or proof of child abuse, patients requiring hospitalization for other reasons

† based mostly prospective trials (not randomized) or large case series

Home observation

PRACTICE GUIDELINE 27-32 HOME OBSERVATION IN MINOR PEDIATRIC HEAD INJURY*

Recommendations†[384]: a child with GCS = 14-15 and normal CT scan‡ can be considered for home observation if neurologically stable

* Definitions: same as in PRACTICE GUIDELINE 27-31

† mostly prospective trials (not randomized) or large case series

‡ these patients are at near zero risk of having an occult brain injury

≈ 22% of those with a history of loss of consciousness **(LOC)** > 5 mins have a brain injury, whereas 92% without LOC > 5 mins will have no brain injury 384.

Outcome

As a group, children fare better than adults with head injury[385]. However, very young children do not do as well as the school-age child[386].

All aspects of neuropsychological dysfunction following head injury may not always be related to the trauma, as children who get injured may have pre-existing problems that increase their propensity to get hurt[387] (this is controversial[388]).

27.15.1. Cephalhematoma

Accumulation of blood under the scalp. Occur almost exclusively in children.

Two types:

1. **subgaleal hematoma**: may occur without bony trauma, or may be associated with linear nondisplaced skull fracture (especially in age < 1 yr). Bleeding into loose connective tissue separates galea from periosteum. May cross sutures. Usually starts as a small localized hematoma, and may become huge (with significant loss of circulating blood volume in age < 1 year, transfusion may be necessary). Inexperienced clinicians may suspect CSF collection under the scalp which does not occur. Usually presents as a soft, fluctuant mass. These do not calcify
2. **subperiosteal hematoma** (some refer to *this* as cephalhematoma): most commonly seen in the newborn (associated with parturition, may also be associated with neonatal scalp monitor[389, 390]). Bleeding elevates periosteum, extent is limited by sutures. Firmer and less ballotable than subgaleal hematoma[391 (p 312)]; scalp moves freely over the mass. 80% reabsorb, usually within 2-3 weeks. Occasionally may calcify

Infants may develop jaundice (hyperbilirubinemia) as blood is resorbed, occasionally as late as 10 days after onset.

Treatment

Treatment beyond analgesics is almost never required, and most usually resolve within 2-4 weeks. Avoid the temptation of percutaneously aspirating these as the risk of infection exceeds the risk of following them expectantly, and in the newborn removal of the blood may make them anemic. Follow serial hemoglobin and hematocrit in large lesions. If a subperiosteal hematoma persists > 6 weeks, obtain a skull film. If the lesion is calcified, surgical removal may be indicated for cosmetic reasons (although with most of these the skull will return to normal contour in 3-6 months[391 (p 315)].

27.15.2. Child abuse

At least 10% of children < 10 yrs age that are brought to E/R with alleged accidents are victims of child abuse[392]. The incidence of accidental head trauma

of significant consequence below age 3 is low, whereas this is the age group in which battering is highest[393].

There are no findings that are pathognomonic for child abuse. Factors which raise the index of suspicion include:

1. retinal hemorrhage (*see below*)
2. bilateral chronic subdural hematomas in a child < 2 yrs age (*see page 905*)
3. skull fractures that are multiple or associated with intracranial injury
4. significant neurological injury with minimal signs of external trauma

SHAKEN BABY SYNDROME

Vigorous shaking of a child produces violent whiplash-like angular acceleration-decelerations of the head (the infant head is relatively large in proportion to the body, and the neck muscles are comparatively weak)[394] which may lead to significant brain injury. Some researchers believe that impact is often also involved[273].

Characteristic findings include retinal hemorrhages (*see below*), subdural hematomas (bilateral in 80%) and/or subarachnoid hemorrhage (SAH). There are usually few or no external signs of trauma (including cases with impact, although findings may be apparent at autopsy). In some cases there may be finger marks on the chest, multiple rib fractures and/or pulmonary compression ± parenchymal lung hemorrhage. Deaths in these cases are almost all due to uncontrollable intracranial hypertension. There may also be injury to the cervicomedullary junction[395].

RETINAL HEMORRHAGE (RH) IN CHILD ABUSE

"In a traumatized child with multiple injuries and an inconsistent history, the presence of RH is pathognomonic of battering"[393]. However, RH may also occur in the absence of any evidence of child abuse. 16/26 battered children < 3 yrs age had RH on funduscopy, whereas 1/32 non-battered traumatized children with head injury had RH (the single false positive: traumatic parturition, where the incidence of RH is 15-30%).

Differential diagnosis of etiologies of retinal hemorrhage:

1. child abuse (including "shaken baby syndrome", *see above*)
2. benign subdural effusion in infants (*see page 904*)
3. acute high altitude sickness (see *High altitude cerebral edema*, page 916)
4. acute increase in ICP: e.g. with a severe seizure (may be similar to

Purtschers retinopathy - *see below*)

5. Purtschers retinopathy[396]: loss of vision following major trauma (chest crush injuries, airbag deployment[397]…), pancreatitis, childbirth or renal failure, among others. Posterior pole ischemia with cotton-wool exudates and hemorrhages around the optic disc due to microemboli of possibly fat, air, fibrin clots, complement-mediated aggregates or platelet clumps. No known treatment

27.16. References

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NOTES

28. Spine injuries

20% of patients with a major spine injury will have a second spinal injury at another level, which may be noncontiguous. These patients often have simultaneous but unrelated injuries (e.g. chest trauma). Injuries directly associated with spinal cord injuries include arterial dissections (carotid and/or vertebral arteries).

TERMINOLOGY

SPINAL STABILITY

A conceptual definition of **clinical stability** from White and Panjabi[1]: the ability of the spine under physiologic loads to limit displacement so as to prevent injury or irritation of the spinal cord and nerve roots (including cauda equina) and, to prevent incapacitating deformity or pain due to structural changes.

Biomechanical stability refers to the ability of the spine *ex vivo* to resist forces.

For models of stability for cervical spine injuries *see page 969*, for thoracolumbar fractures *see page 986*.

LEVEL OF INJURY

There is disagreement over what should be defined as "the level" of a spinal cord injury. Some use the lowest level of completely normal function. However, most sources define the "level" as the most caudal segment with motor function that is at least 3 out of 5 and if pain and temperature sensation is present.

COMPLETENESS OF LESION

Incomplete lesion

Definition: any residual motor or sensory function more than 3 segments below the level of the injury[2]. Look for signs of preserved long-tract function.

Signs of incomplete lesion:

- sensation (including position sense) or voluntary movement in the LEs

- "**sacral sparing**": preserved sensation around the anus, voluntary rectal sphincter contraction, or voluntary toe flexion
- an injury does not qualify as incomplete with preserved sacral reflexes alone

Types of incomplete lesion:
- central cord syndrome: *see page 948*
- Brown-Séquard syndrome (cord hemisection): *see page 950*
- anterior cord syndrome: *see page 950*
- posterior cord syndrome: rare, *see page 951*

Complete lesion

No preservation of any motor and/or sensory function more than 3 segments below the level of the injury. About 3% of patients with complete injuries on initial exam will develop some recovery within 24 hours. Recovery is essentially zero if the spinal cord injury remains complete beyond 72 hours.

SPINAL SHOCK

This term is often used in two completely different senses:

1. hypotension (shock) that follows spinal cord injury (SBP usually ≈ 80 mm Hg). See *Hypotension* page 935 for treatment. Caused by multiple factors:
   A. interruption of sympathetics: implies spinal cord injury **above T1**
      1. loss of vascular tone (vasoconstrictors) below level of injury
      2. leaves parasympathetics relatively unopposed causing bradycardia
   B. loss of muscle tone due to skeletal muscle paralysis below level of injury results in venous pooling and thus a *relative* hypovolemia
   C. blood loss from associated wounds → true hypovolemia
2. transient loss of all neurologic function (including segmental and polysynaptic reflex activity and autonomic function) below the level of the SCI[3, 4] → flaccid paralysis and areflexia lasting varying periods (usually 1-2 weeks, occasionally several months and sometimes permanently), the resolution of which yields the anticipated spasticity below the level of the lesion. A poor prognostic sign. Spinal cord reflexes immediately above the injury may also be depressed on the basis of the Schiff-Sherrington phenomenon

28.1. Whiplash-associated disorders

“Whiplash” was initially a lay term, which is currently defined as a traumatic injury to the soft tissue structures in the region of the cervical spine (including: cervical muscles, ligaments, intervertebral discs, facet joints…) due to hyperflexion, hyperextension, or rotational injury to the neck in the absence of fractures, dislocations, or intervertebral disc herniation[5]. It is the most common non-fatal automobile injury[6]. Symptoms may start immediately, but more commonly are delayed several hours or days. In addition to symptoms related to the cervical spine, common associated complaints include headaches, cognitive impairment, and low back pain.

A proposed clinical classification system of WAD is shown in *Table 28-1*. A consensus regarding diagnosis and management of these injuries is shown in *Table 28-2* and *Table 28-3*. Keep in mind that conditions such as occipital neuralgia may occasionally follow whiplash type injuries and should be treated appropriately (*see page 804*).

Table 28-1 Clinical grading of WAD severity

Grade		Description
0		no complaints, no signs*
WHIPLASH	1	neck pain or stiffness or tenderness, no signs
	2	above symptoms with reduced range of motion or point tenderness
	3	above symptoms with weakness, sensory deficit, or absent deep tendon reflexes
4		above symptoms with fracture or dislocation*

* the definition of whiplash excludes these patients[5]

Table 28-2 Evaluation of WAD

Grade 1 patients with normal mental status and physical exam do not require plain radiographs on presentation
Grade 2 & 3 patients: C-spine x-rays, possibly with flexion-extension views. Special imaging studies (MRI, CT, myelography…) are not indicated
Grade 3 & 4: these patients should be managed as suspected spinal cord injury *(see Initial management of spinal cord injury* below, and sections that follow)

Table 28-3 Treatment of WAD[7]*

Whiplash is usually a benign condition requiring little treatment & resolves in days to a few weeks in most cases.			
Recommendation	**Grade**		
	1	2	3
Range of motion exercises	should be started immediately for all		
Encourage early return to regular activities	immediately	ASAP	
Cervical collars and rest†	no	not for > 72 hrs	not for > 96 hrs
Passive modality therapies: heat, ice, massage, TENS, ultrasound, relaxation techniques, acupuncture, and work alteration	no	optional if symptoms last > 3 wks	
Medications: optional use of NSAIDs and non-narcotic analgesics? (recommended for ≤ 3 wks)	no	yes	yes. Limited narcotics may also occasionally be needed
Surgery	no	no	only for progressive neurologic deficit or persisting arm pain
✖ **Not** recommended: cervical pillows and soft collars, bed rest, spray and stretch exercises, muscle relaxant medication, TENS, reflexology, magnetic necklaces, herbal remedies, homeopathy, OTC medications (except NSAIDs, *see above*), and intra-articular, intrathecal, or trigger point steroid injections			

* excluding patients with fractures, dislocations, or spinal cord injuries

† soft foam collars are generally discouraged; if they are to be used, the narrow part should be placed in front to avoid neck extension[5]

Outcome

In a study of 117 patients < 56 years of age having WAD due to automobile accidents (excluding those with cervical fractures, dislocations, or injuries elsewhere in the body) conducted in Switzerland[8] (where all medical costs were paid by the state and there was no opportunity for litigation and no compensation for pain and suffering, although there was the possibility of permanent disability), the recovery rate was as shown in *Table 28-4*. Of the 21 patients with continued symptoms at 2 yrs, only 5 were restricted with respect to work (3 reduced to part-time work, 2 on disability). Patients with persistent symptoms were older, had more varied complaints on initial exam, had a more rotated or inclined head position at the time of impact, had a higher incidence of pretraumatic headaches, and had a higher incidence of certain pre-existing findings (such as radiologic evidence of cervical osteoarthritis). The amount of damage to the automobile and the speed of the cars has little relationship to the degree of injury, and outcome was not influenced by gender, vocation, or psychological factors.

Table 28-4 Recovery of patients with WAD

Time (mos)	Percent recovered
3	56%
6	70%

12	76%
24	82%

28.2. Pediatric spine injuries

Spinal cord injury is fairly uncommon in children, with the ratio of head injuries to spinal cord injuries being ≈ 30:1 in pediatrics. Only ≈ 5% of spinal cord injuries occur in children. Due to ligamentous laxity together with a high head to body weight ratio, immaturity of paraspinal muscles and the underdeveloped uncinate processes, these tend to involve ligamentous rather than bony injuries (*see* SCIWORA, *page 974*). The cervical spine is the most vulnerable segment (with subaxial injuries being fairly uncommon), with 42% of injuries occurring here, 31% thoracic, and 27% lumbar. The fatality rate is higher with pediatric spine injuries than with adults (opposite to the situation with head injury), with the cause of death more often related to other severe injuries than to the spinal injury[9].

PRACTICE GUIDELINE 28-1 PEDIATRIC C-SPINE INJURIES

Diagnosis

Level II[10]: C-spine x-rays are <u>not</u> indicated in pediatric trauma patients who are:

- alert & conversant
- neurologically intact
- without posterior midline cervical tenderness (with no distracting pain)
- and who are not intoxicated

Level III[10]: for pediatric trauma patients who are: nonconversant or have altered mental status, neurologic deficit, neck pain or a painful distracting injury, are intoxicated, or have unexplained hypotension:

- patients < 9 yrs: AP & lateral C-spine x-rays
- patients ≥ 9 yrs: open-mouth odontoid view in addition to the above
- supplement these x-rays with additional thin cut CT through areas of suspicion or areas not visualized on plain x-ray
- flexion-extension C-spine x-rays or fluoroscopy may be considered to R/O ligamentous instability if there is still a suspicion of instability after the

above x-rays are obtained
- consider: C-spine MRI to R/O cord or nerve root compression, evaluate ligamentous integrity, or provide information for neurologic prognosis

Treatment

Level III[10]:
- children < 8 yrs age: immobilize with thoracic elevation or an occipital recess (allows more neutral alignment due to the relatively large head)
- children < 7 yrs age with injuries of the C2 dentocentral synchondrosis (*see page 137*): closed reduction and halo immobilization
- consider: primary operative treatment for isolated C-spine ligamentous injuries with associated deformity

PEDIATRIC CERVICAL SPINE INJURIES

For pediatric C-spine anatomy *see page 137*. In the age group ≤ 9 yrs, 67% of cervical spine injuries occur in the upper 3 segments of the cervical spine (occiput-C2)[11].

SYNCHONDROSES (*see page 137*)

Normal synchondroses may be mistaken for fractures (especially the dentocentral synchondrosis of the atlas (*see page 137*) which may be mistaken for an odontoid fracture). Conversely, actual fractures may occur through synchondroses[12, 13]. Recommended treatment for fractures through synchondroses: the tendency for synchondroses to fuse suggests that emergency reduction followed by external immobilization be attempted. Internal immobilization/fusion should be reserved for persistent instability[13].

PSEUDOSPREAD OF THE ATLAS[14]

Pseudospread of the atlas (defined as > 2 mm total overlap of the two C1 lateral masses on C2 on AP open-mouth view) is present in most children 3 mos to 4 yrs age. Prevalence is 91-100% during the second year of life. Youngest example at 3 mos, oldest at 5.75 yrs. Normal total offset is typically 2 mm during the first year, 4 mm during the second, 6 mm during the third, and decreasing thereafter. The maximum is 8 mm. Trauma is not a contributing factor.

Pseudospread is probably a result of disproportionate growth of the atlas on the axis. This could be misdiagnosed as a Jefferson fracture (*see page 958*),

which rarely occurs prior to the teenages (owing to lower weight of children, more flexible necks, increased plasticity of skull, and shock absorbing synchondroses of C1).

Neck rotation can also sometimes simulate the appearance of a Jefferson fracture.

When suspicion of fracture is high: CT scan through C1 can resolve the issue of whether or not there is a fracture.

Pseudosubluxation

Either anterior displacement of C2 (axis) on C3 and/or significant angulation at this level. Seen in children (up to age 10 yrs) on lateral C-spine x-ray after trauma. Up to age 10 yrs, flexion and extension are centered at C2-3; this moves down to C4-5 or C5-6 after age 10. C2 normally moves forward on C3 up to 2-3 mm in peds[15]. When the head is flexed, displacement is expected; may be exacerbated by spasm[16]. Does not represent pathological instability. Fractures and dislocations are unusual in children, and when they do occur, they resemble those in adults.

10 cases reported between ages 4-6 yrs[17]: pain was not uncommon. In each case, either the head or neck was flexed (sometimes minimally); the pseudosubluxation corrected when x-ray was repeated with head in true neutral position.

Recommendation: treat patient for soft-tissue injury and not for subluxation.

28.3. Initial management of spinal cord injury

The major causes of death in spinal cord injury **(SCI)** are aspiration and shock[4]. Initial survey under ATLS protocol: assessment of airway takes precedence, then breathing, then circulation & control of hemorrhage (“ABC’s”). This is followed by a brief neurologic exam.

NB: other injuries (e.g. abdominal injuries) may be masked below the level of SCI.

Any of the following patients should be treated as having a SCI until proven otherwise:

1. all victims of significant trauma
2. trauma patients with loss of consciousness
3. minor trauma victims with complaints referable to the spine (neck or back

pain or tenderness) or spinal cord (numbness or tingling in an extremity, weakness)

4. associated findings suggestive of SCI include
   A. abdominal breathing
   B. priapism (autonomic dysfunction)

The orientation of the management differs based on the patient's situation as follows:

1. no history of significant trauma, completely alert, oriented and free of drug or alcohol intoxication with no complaints referable to the spine: most may be cleared clinically without the need for C-spine x-rays
2. significant trauma, but no strong evidence of spine or spinal cord injury: the emphasis here is in ruling-out a bony lesion and preventing injury
3. patients with neurologic deficit: the emphasis here is to define the skeletal injury and to take steps to prevent further cord injury and loss of function and minimize or reverse the present deficit. The pros and cons of the high-dose methylprednisolone protocol (*see page 936*) should be weighed if a neurologic deficit is identified

Clinical criteria to rule-out cervical spine instability

To date, there has not been a case of a significant occult cervical spine injury[18, 19] in a trauma patient who met all of the criteria in *Table 28-5*[A].

A. although reports of bony or ligamentous abnormalities have be described as possibly occurring in these patients, there has been no report of a patient who had neurologic injury as a result of these abnormalities

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Table 28-5 Clinical criteria for cervical spine stability

1. awake, alert, oriented (no mental status changes, including no alcohol or drug intoxication)
2. no neck pain (with no distracting pain)
3. no neurologic deficits

Table 28-6 NATA helmet removal guidelines*

✖ NB: do not remove the helmet in the field.
• most injuries can be visualized with the helmet in place • neurological exam can be done with the helmet in place • the patient may be immobilized on a spine board with the helmet in place • the facemask can be removed with special tools to access the airway

• hyperextension must be avoided following removal of the helmet and shoulder pads
In a controlled setting (usually after x-rays) the helmet and shoulder-pads are removed together as a unit to avoid neck flexion or extension
Possible indications for removal of helmet
• face mask cannot be removed in a reasonable amount of time • airway cannot be established even with face mask removed • life threatening hemorrhage under the helmet that can be controlled only by removal • helmet & strap do not hold head securely so that immobilizing the helmet does not adequately immobilize the spine (e.g. poor fitting or damaged helmet) • helmet prevents immobilization for transportation in an appropriate position • certain situations where the patient is unstable (M.D. decision)

* for more details, see http://www.nata.org

MANAGEMENT IN THE FIELD

1. immobilization prior to and during extrication from vehicle and transport to prevent active or passive movements of the spine. For possible C-spine injuries in football players, *see Table 28-6* for the National Athletic Trainers' Association (NATA) guidelines for helmet removal. When CPR is necessary it takes precedence. Caution with intubation (*see below*)
   A. log-roll patient to turn
   B. place patient on back-board
   C. sandbags on both sides of the head with a 3 inch strip of adhesive tape from one side of the back-board to the other across the forehead immobilizes the spine as well as a rigid orthosis[20] but allows movement of the jaw and access to the airway
   D. a rigid cervical collar (e.g. Philadelphia collar) may be used to supplement
2. maintain blood pressure (*see below* under *Hypotension*)
   A. pressors: treats the underlying problem (essentially a traumatic sympathectomy). Dopamine is the agent of choice, and is preferred over fluids (except as necessary to replace losses) (see *Cardiovascular agents for shock*, page 22 for pressors). ✖ Avoid phenylephrine (*see below*)
   B. fluids as necessary to replace losses
   C. military anti-shock trousers (MAST): immobilizes lower spine, compensates for lost muscle tone in cord injuries (prevents venous pooling)
3. maintain oxygenation (adequate FIO_2 and adequate ventilation)
   A. if no indication for intubation: use NC or face mask

B. intubation
   1. indications: may be required for
      a. airway compromise
      b. hypopnea:
         i. from paralyzed intercostal muscles
         ii. from paralyzed diaphragm (phrenic nerve = C3, 4 & 5)
         iii. or from depressed LOC
   2. caution with intubation with uncleared C-spine
      a. use chin lift (not jaw thrust) without neck extension
      b. nasotracheal intubation may avoid movement of C-spine but patient must have spontaneous respirations
      c. avoided tracheostomy or cricothyroidotomy if possible (may compromise later anterior cervical spine surgical approaches)

4. brief motor exam to identify possible deficits (also to document delayed deterioration); ask patient to:
   A. move arms
   B. move hands
   C. move legs
   D. move toes

MANAGEMENT IN THE HOSPITAL

Basic phases of management with respect to the spine:
1. stabilization (medical & spinal), preliminary evaluation & treatment
2. evaluation of spinal stability
3. subsequent (definitive) treatment

PRACTICE GUIDELINE 28-2 ASSESSMENT OF SCI IN THE HOSPITAL

Clinical Assessment

Level III[21]: the ASIA international standards for neurological and functional assessment of spinal cord injury **(SCI)** (*see page 945*) is recommended

Functional outcome assessment

Level II[21]: the Functional Impairment Measure™ **(FIM™)** (*see page 1184*) is recommended

Level III[21]: the modified Barthel index (*see page 1183*) is recommended

PRACTICE GUIDELINE 28-3 IN-HOSPITAL CRITICAL CARE MANAGEMENT OF SCI

Level III[22]: monitor patients with acute SCI (especially those with severe cervical level injuries) in an ICU or similar monitored setting
Level III[22]: cardiac, hemodynamic & respiratory monitoring after acute SCI is recommended
Level III[23]: hypotension (SBP < 90 mm Hg) should be avoided or corrected ASAP
Level III[23]: maintain MAP at 85-90 mm Hg for the first 7 days after SCI to improve spinal cord perfusion

STABILIZATION AND INITIAL EVALUATION

1. immobilization: maintain backboard/head-strap (*see above*) to facilitate transfers to CT table, etc. Once studies are completed, remove patient from backboard by logrolling (early removal from board reduces risk of decubitus ulcers)
2. hypotension (spinal shock): maintain SBP ≥ 90 mm Hg. Spinal cord injuries cause hypotension by a combination of factors (*see page 930*) which may further injure spinal cord[24] or other organ systems
   A. pressors if necessary: dopamine is agent of choice (✖ avoid phenylephrine: non-inotropic and possible reflex increase in vagal tone with bradycardia)
   B. careful hydration (abnormal hemodynamics → propensity to pulmonary edema)
   C. atropine for bradycardia associated with hypotension
3. oxygenation (*see above*)
4. NG tube to suction: prevents vomiting and aspiration, and decompresses abdomen which can interfere with respirations if distended (paralytic ileus is common, and usually lasts several days)
5. indwelling (Foley) urinary catheter: for I's & O's and to prevent distension from urinary retention
6. DVT prophylaxis: *see below*
7. temperature regulation: vasomotor paralysis may produce poikilothermy

(loss of temperature control), this should be treated as needed with cooling blankets

8. electrolytes: hypovolemia and hypotension cause increased plasma aldosterone which may lead to hypokalemia
9. more detailed neuro evaluation (see *ASIA (American Spinal Injury Association) motor scoring system*, page 945). Patients may be stratified using the ASIA impairment scale (see *Table 28-13*, page 947)
   A. focused history: key questions should center on:
      1. mechanism of injury (hyperflexion, extension, axial loading…)
      2. history suggestive of loss of consciousness
      3. history of weakness in the arms or legs following the trauma
      4. occurrence of numbness or tingling at any time following the injury
   B. palpation of the spine for point tenderness, a "step-off", or widened interspinous space
   C. motor level assessment
      1. skeletal muscle exam (can localize dermatome)
      2. rectal exam for voluntary anal sphincter contraction
   D. sensory level assessment
      1. sensation to pinprick (tests spinothalamic tract, can localize dermatome): be sure to test sensation in face also (spinal trigeminal tract can sometimes descend as low as ≈ C4)
      2. light (crude) touch: tests anterior cord (anterior spinothalamic tract)
      3. proprioception/joint position sense (tests posterior columns)
   E. evaluation of reflexes
      1. muscle stretch reflexes: usually absent initially in cord injury
      2. abdominal cutaneous reflexes
      3. cremasteric reflex
      4. sacral
         a. bulbocavernosus: *see footnote, page 946*
         b. anal-cutaneous reflex
   F. examine for signs of autonomic dysfunction
      1. altered patterns of perspiration (abdominal skin may have low coefficient of friction above lesion, and may seem rough below due to lack of perspiration)
      2. bowel or bladder incontinence
      3. priapism: persistent penile erection

10. radiographic evaluation: *see below*
11. medical management specific to spinal cord injury:
    A. methylprednisolone (*see below*)
    B. experimental/investigational drugs: none of these agents shown to have un-equivocal benefit in man: naloxone, DMSO, Lazaroid®. Tirilazad mesylate (Freedox®) was less beneficial than methylprednisolone[25]

METHYLPREDNISOLONE

PRACTICE GUIDELINE 28-4 METHYLPREDNISOLONE IN SCI

★ Still highly controversial even among experts[26-28]
Level III: treatment with methylprednisolone for 24 or 48 hrs after SCI is an option that should be undertaken only with the knowledge that the evidence suggesting harmful side effects is more consistent than any demonstrated clinical benefit

It has been asserted that beneficial (sensory and motor) effects at 6 weeks, 6 months and 1 year are seen (for both complete and incomplete injuries) when methylprednisolone **(MP)** is administered as shown below, but only if given **within 8 hours** of injury (NB: outcome is possibly worse at 1 year if the drug is started after 8 hrs from injury)[29, 30]. See *Critique* below.

Exclusionary criteria from the study (these patients were not studied, and no determination was made whether the drug was helpful or not, or safe or not):
1. cauda equina syndrome (*see page 446*)
2. gunshot wounds **(GSW)** to the spine: a retrospective study showed no benefit and increased risk of complications with steroids with GSW[31]
3. life-threatening morbidity
4. pregnancy
5. narcotic addiction
6. age < 13 years
7. patient on maintenance steroids

Administration

1. **concentration**: in the following protocol, all solutions are mixed as 62.5

mg/ml (e.g. by diluting 16 gm methylprednisolone with bacteriostatic water to 256 ml)

2. **bolus**: 30 mg/kg initial IV bolus over 15 minutes, infused as shown in *Eq 28-1* with an IV controller (this delivers 0.48 ml/kg of solution in 15 minutes):

$$\boxed{\text{bolus rate (ml/hr)} = \text{patient s weight (kg) X 1.92} \quad \text{(for 15 minutes)}} \qquad \textbf{Eq 28-1}$$

3. followed by a 45 minute pause
4. **maintenance infusion**: then 5.4 mg/kg/hr continuous infusion as shown in *Eq 28-2* (infusion is maintained during any necessary surgery if possible)

$$\boxed{\text{maintenance rate (ml/hr)} = \text{patient s weight (kg) X 0.0864} \quad \text{(for 23 or 47 hours*)}} \qquad \textbf{Eq 28-2}$$

* **duration** of maintenance infusion: when therapy is initiated ≤ 3 hrs after injury, the infusion is administered for 23 hrs. If therapy is started between 3 and 8 hrs of injury, there may be an incremental benefit in 47 hrs of infusion, with slightly higher risk of infection and pneumonia[25]

Critique

A metaanalysis[32] of the literature could not identify any study that replicated the results of the original studies. At 1 year the MP group only showed a slight sensory advantage over the placebo group. Furthermore, high-dose MP may cause acute corticosteroid myopathy[33] **(ACM)** which might indicate that some patients that improved after MP were actually recovering from their ACM. ACM and it's associated complications (prolonged ventilator dependency…) should be added to the list of potential complications of high-dose MP (hyperglycemia, pneumonia, sepsis).

Hypothermia for Spinal Cord Injury

The position statement of the joint sections of the AANS and the CNS is that there is not enough evidence to recommend for or against local or systemic hypothermia for acute SCI, and that it should be noted that systemic hypothermia is associated with medical complications in TBI[34].

Deep-Vein Thrombosis in Spinal Cord Injuries

Also see *Thromboembolism in neurosurgery*, page 42. Incidence of DVT may be as high as 100% when 125I-fibrinogen is used[35]. Overall mortality from DVT is 9% in SCI patients.

PRACTICE GUIDELINE 28-5 DVT IN PATIENTS WITH CERVICAL SCI

Level I[36]: prophylactic treatment of thromboembolism in patients with severe motor deficits due to SCI. Choices include:

- LMW heparin, rotating beds, adjusted dose heparin, or some combination of these measures
- or, low-dose heparin + pneumatic compression stockings or electrical stimulation

Level II[36]:

✖ not recommended: low-dose heparin used alone

✖ not recommended: oral anticoagulation alone

Level III[36]:

- duplex doppler ultrasound, impedance plethysmography & venography are recommended as diagnostic tests for DVT in patients with SCI
- vena cava interruption filters for patients who do not respond to, or are not candidates for, anticoagulation

PROPHYLAXIS

Study of 75 patients found titrating dose of SQ heparin q 12 hrs to a PTT of 1.5 times control resulted in lower incidence of thromboembolic events (DVT, PE) than "mini-dose" heparin (5000 U SQ q 12 hrs) (7% vs. 31%)[37]. Heparin can cause thrombosis, thrombocytopenia and chronic therapy may produce osteoporosis (see *heparin*, page 39).

RADIOGRAPHIC EVALUATION AND INITIAL C-SPINE IMMOBILIZATION

PRACTICE GUIDELINE 28-6 X-RAYS IN TRAUMA PATIENTS

Asymptomatic trauma patients

Level I[38] & **Level II**[39]: radiographic studies are not indicated* in patients who have:

- no mental status changes† (and no evidence of alcohol or drugs‡)
- no neck pain or posterior midline tenderness (and no distracting pain)
- no focal neurologic deficit (on motor or sensory exam)

- and who do not have significant associated injuries that detract from their general evaluation

Trauma patients who are symptomatic, or obtunded or have unreliable exam (altered mental status, distracting injuries…)

Level II[39]: the primary screening modality is thin-cut axial CT from the occiput to T1 with sagittal and coronal reconstructions
Level II[39]: plain x-rays add no information and should not be done§

* these are basically the 5 NEXUS criteria from Hoffman et al.[40]: no midline cervical tenderness, no focal neuro deficit, normal alertness, no intoxication, no painful distracting injury. The Canadian C-Spine Rule (CCR) was found to be more sensitive & specific[41], but the EAST has not embraced it as of this writing[39]

† altered mental status can include GCS ≤ 14; disorientation to person, place, time or events; inability to remember 3 objects at 5 minutes; delayed response to external stimuli

‡ evidence of alcohol or drugs includes information from the history, physical findings (slurred speech, ataxia, odor of alcohol on the breath) or positive blood or urine tests

§ unless CT scan is not available or contraindicated

PRACTICE GUIDELINE 28-7 CERVICAL IMMOBILIZATION IN TRAUMA PATIENTS

A cervical collar is not needed in trauma patients who meet these criteria

- awake, alert, without neurologic deficit or distracting injury who have no <u>neck pain</u> or tenderness and full ROM of the cervical spine (**Level II**[39])
- penetrating brain trauma: unless the trajectory suggests direct cervical spine injury (**Level III**[39])
- **Level III**[42] & **Level III**[39]: awake <u>with</u> neck pain or tenderness and normal cervical CT scan after either*
  1. normal & adequate dynamic flexion-extension C-spine x-rays
  2. or a normal cervical MRI† is obtained‡

In <u>obtunded</u> patients with normal cervical CT scan and gross movement of all 4 extremities

- ✖ flexion-extension C-spine x-rays should <u>not</u> be performed (**Level II**[39])
- options:

1. maintain cervical collar until a clinical exam can be performed[39]
2. remove the collar on the basis of the normal CT scan alone[39§]
3. obtain cervical MRI[†]: the risk and benefit of cervical MRI in addition to CT is unclear, and must be individualized (**Level III**[39]). If the MRI is normal, the collar may be safely removed (**Level II**[39])

* these tests are performed in the absence of an identifiable fracture or obviously unstable dislocation to rule-out ligamentous or other soft-tissue injury that might be occult and unstable

† AANS/CNS guidelines from 2002 recommended getting the MRI within 48 hours[42]

‡ MRI is usually employed in this setting when the patient is unable to cooperate for flex-ext x-rays. For MRI findings and issues related to timing, etc., *see page 941*

§ the incidence of ligamentous injury with negative CT is < 5%, and the incidence of clinically significant injury is unknown but is much < 1%[39]

Cervical immobilization

Cervical collars should be removed as soon as it can be determined that it is safe to do so. The benefits from early collar removal include: reduction of skin breakdown[43], fewer days of mechanical ventilation[44], shorter ICU stays[44], reduction of ICP[45, 46].

Minimal radiographic evaluation

There is controversy regarding what constitutes a minimal radiographic evaluation of the cervical spine in multiple trauma patient. No imaging modality is 100% accurate.

Asymptomatic patients (meeting criteria outlined in *PRACTICE GUIDELINE 28-6*) may be considered to have a stable cervical spine and <u>no</u> radiographic studies of the cervical spine are indicated[39, 42]. Factors associated with increased risk of failing to recognize spinal injuries include: decreased level of consciousness (due to injury or drugs/alcohol), multiple injuries, technically inadequate x-rays[47] (also, see *Delayed cervical instability*, page 982).

2009 recommendation of the Eastern Association for the Surgery of Trauma **(EAST)** is that the primary screening modality is thin-cut axial CT from the occiput to T1 with sagittal and coronal reconstructions[39] which is more accurate than plain radiographs.

When CT scan is not appropriate as the initial screening exam, the following guidelines are offered:

See *X-rays, C-Spine* on page 135 for normal vs. abnormal findings. *Table 28-*

7 lists some indicators that should alert the reviewer that there may be significant C-spine trauma (they do not indicate definite instability by themselves).

1. cervical spine: must be cleared radiographically from the cranio-cervical junction down through and including the C7-T1 junction (incidence of pathology at C7-T1 junction may be as high as 9%[48]):
   A. lateral portable C-spine x-ray while in rigid collar: this study by itself will miss ≈ 15% of injuries[50]
   B. if all 7 cervical vertebra AND the C7-T1 junction are adequately visualized and are normal, and if the patient has no neck pain or tenderness and is neurologically intact[A], then remove the cervical collar and complete the remainder of the cervical spine series (AP and open-mouth odontoid **(OMO)** view). Lateral, AP, and OMO views together detect essentially all unstable fractures in intact[A] patients[51] (although the AP view rarely provides unique information[52]). In a severely injured patient, limitation to an AP and lateral view usually suffices for the acute (but not complete) evaluation[53]
   C. if the above studies are normal, but there is neck pain, tenderness or neurologic findings (there may be a spinal cord injury even with normal plain films), or if the patient is unable to reliably verbalize neck pain or cannot be examined for neurologic deficit, then further studies are indicated, which may include any of the following:
      1. **oblique views**[B]: demonstrates the neural foramina (may be blocked with a unilateral locked facet (*see page 973*)), and helps assess the integrity of the articular masses and lamina (the lamina should align like shingles on a roof)[53]
      2. flexion-extension views: *see below*
      3. CT scan: helpful in identifying bony injuries. However, CT cannot exclude significant soft-tissue or ligamentous injury[54]
      4. MRI: utility is limited to specific situations (*see page 941*) and the accuracy has not been determined
      5. polytomograms: becoming less available
      6. **pillar view**: devised to demonstrate the cervical articular masses en face (reserved for cases suspected of having articular mass fracture)[55]: the head is rotated to one side (requires that the upper cervical spine injury has been excluded by previous radiographs), the x-ray tube is off centered 2 cm from midline in the opposite direction and the beam is angled 25° caudad, centered at the

superior margin of the thyroid cartilage

7. if subluxation is present at any level and is $\leq$ **3.5 mm** and the patient is neurologically intact[A], obtain flexion-extension films (*see below*)
8. if no pathologic movement, may discontinue cervical collar
9. even if no instability is demonstrated, may need delayed films once pain and muscle spasms have resolved to reveal instability

D. if <u>lower</u> C-spine (and/or cervical-thoracic junction) are not well visualized
  1. repeat lateral C-spine x-ray with caudal traction on the arms (if not contraindicated based on other injuries, e.g. to shoulders)
  2. if still not visualized, then obtain a “swimmer’s” (Twining) view: the x-ray tube is positioned above the shoulder furthest from the film, and aimed towards the axilla closest to the film with the tube angled 10-15° toward the head while the arm is elevated above the head
  3. if still not visualized: CT scan through non-visualized levels (CT is poor for evaluating alignment and for fractures in the horizontal plane, thin cuts with reconstructions ameliorates this shortcoming)

E. for questions regarding stability of the subaxial spine, *see page 969*

F. patients with C-spine fractures or dislocations should have daily C-spine x-rays during initial traction or immobilization

2. thoracic and lumbosacral spine: AP and lateral x-rays for all trauma patients who:
  A. were thrown from a vehicle, or fell $\geq$ 6 feet to the ground
  B. complain of back pain
  C. are unconscious
  D. are unable to reliably describe back pain or have altered mental status preventing adequate exam
  E. have an unknown mechanism of injury, or other injuries that cast suspicion of spine injury
3. reminder: when abnormalities of questionable vintage are identified, a bone scan may be helpful to distinguish an old injury from an acute one (less useful in the elderly; in an adult, a bone scan will become “hot” within 24-48 hrs of injury, and will remain hot for up to a year; in the elderly, the scan may not become hot for 2-3 weeks and can remain so for over a year)
4. CT scan through area of bony abnormality or level of neurologic deficit

(*see below*)

A. neurologically intact implies patient is alert, not drugged/intoxicated, & able to report pain reliably
B. some authors include oblique views in a "minimal" evaluation[53], others do not[51]

Table 28-7 Radiographic signs of C-spine trauma (modified[49])

Soft tissues
• retropharyngeal space > 7 mm, or retrotracheal space > 14 mm (adult) or 22 mm (peds) (see *Table 6-10*, page 137 for details) • displaced prevertebral fat stripe • tracheal deviation & laryngeal dislocation
Vertebral alignment
• loss of lordosis • acute kyphotic angulation • torticollis • widened interspinous space (flaring) • axial rotation of vertebra • discontinuity in contour lines (*see page 135*)
Abnormal joints
• ADI: > 3 mm (adult) or > 4 mm (peds) (see *Table 6-9*, page 136 for details) • narrowed or widened disc space • widening of apophyseal joints

FLEXION-EXTENSION CERVICAL SPINE X-RAYS

Purpose: to disclose occult ligamentous instability.

It is possible to have a purely ligamentous injury involving the posterior ligamentous complex without any bony fracture (see *Hyperflexion sprain*, page 971). Lateral flexion-extension views help detect these injuries, and also evaluate other injuries (e.g. compression fracture) for stability. For patients with limited flexion due to paraspinal muscle spasm (sometimes resulting from pain), a rigid collar should be prescribed, and if the pain persists 2-3 weeks later[56] the flexion-extension films should be repeated.

✖ Contraindications

1. the patient must be cooperative and free of mental impairment (i.e. no head injury, street or prescription drugs, alcohol…)
2. there should not be any subluxation **> 3.5 mm** at any level on cross-table C-spine x-rays (which is a marker for possible instability, *see page 972*)
3. patient must be neurologically intact (if there is any degree of spinal cord

injury, proceed instead first with imaging studies, e.g. MRI)

4. F/E x-rays are no longer recommended in obtunded patients due to a low yield, poor cost-effectiveness, and they may be dangerous[39]

Technique

The patient should be sitting, and is instructed to flex the head slowly, and to stop if it becomes painful. Serial x-rays are taken at 5-10° increments (or followed under fluoro with spot films at the end of movement), and if normal, the patient may be encouraged to flex further. This is repeated until evidence of instability is seen, or the patient cannot flex further because of pain or limitation of motion. The process is then repeated for extension.

Findings

Normal flexion-extension views demonstrate slight anterior subluxation distributed over all cervical levels with preservation of the normal contour lines (see *Figure 6-2*, page 135). Abnormal findings include: “flaring” of the spinous processes - exaggerated widening (*see page 137*).

CT SCAN

Obtained through levels of abnormality identified on plain films or myelogram, or at level of neurologic deficit in patients with normal films, or at levels inadequately evaluated by plain films. Thin cuts (1.5-3 mm) through the level of suspicion are required. Assesses bony anatomy in detail. When combined with intrathecal contrast (i.e. after myelogram), also delineates any neural impingement.

EMERGENT MRI (OR MYELOGRAM)

Indications for emergent MRI in spinal cord injury **(SCI)** are listed below.

When MRI cannot be performed a myelogram is required (employing intrathecal water soluble contrast with CT to follow) ✖ Caution: cervical myelogram in patients with cervical spine injuries usually requires C1-2 puncture to achieve adequate dye concentration in the cervical region without dangerous extension of the neck or tilting of the patient as required when dye is injected via LP. Furthermore, pressure shifts from LP exacerbates deficit in 14% of cases with complete block[57].

Indications:

1. incomplete SCI with normal alignment: to check for soft tissue compressing cord
2. neurologic deterioration (worsening deficit or rising level) including after closed reduction
3. neurologic deficit not explained by radiographic findings, including:
   A. fracture level different from level of deficit
   B. no bony injury identified: further imaging is done to R/O soft tissue compression (disc herniation, hematoma…) that would require surgery
   C. always consider possible arterial dissection in this setting (*see page 1160*)

MRI *(NON-EMERGENT)*

MRI may be used to identify potentially unstable occult ligamentous or soft tissue injury. Note: abnormal signal on MRI is not always associated with instability on flexion-extension x-rays[58]. It has been recommended that this MRI should be done within 48 hours[42] or 72 hrs[59] of injury. MRI is not reliable for identifying osseous injury. Indications for non-emergent MRI (modified[60]):

1. inconclusive cervical spine radiography, including questionable fractures
2. significant midline paraspinal tenderness and patient unable to have flexion-extension x-rays
3. obtunded or comatose patients

T2WI and FLAIR are the most helpful sequences. Significant abnormal findings:

1. ventral signal abnormalities with prevertebral swelling
2. dorsal signal abnormalities. Abnormal signal limited to the interspinous is probably not as unstable as when it extends into the ligamentum flavum[60]. These patients were treated with rigid collars or Minerva jackets for 1-3 months, and one that was felt to be very unstable underwent fusion
3. disc disruption indicated by abnormal signal intensity within the disc, increased disc height, or frank disc protrusions

TRACTION/REDUCTION OF CERVICAL SPINE INJURIES

Purpose

To reduce fracture-dislocations, maintain normal alignment and/or immobilize the cervical spine to prevent further spinal cord injury. Reduction decompresses the spinal cord and roots, and may facilitate bone healing.

PRACTICE GUIDELINE 28-8 INITIAL CLOSED REDUCTION IN FRACTURE/DISLOCATION CERVICAL SCI

Level III[61]

- early closed reduction of C-spine fracture/dislocation injuries with craniocervical traction to restore anatomic alignment in awake patients

✖ not recommended: closed reduction in patients with an additional rostral injury

- patients with C-spine fracture-dislocation who cannot be examined during attempted closed reduction, or before open posterior reduction, should undergo cervical MRI before attempted reduction*. The presence of a significant herniated disc in this setting is a relative indication for anterior decompression before reduction
- cervical MRI is also recommended for patients who fail attempts at closed reduction*

* NB: prereduction MRI will show disrupted or herniated discs in 33-50% of patients with facet subluxation. These findings do not seem to significantly influence outcome after closed-reduction in awake patients; ∴ the usefulness of prereduction MRI in this setting is uncertain

Controversies

1. the rapidity with which reduction should be done[4]
2. whether MRI should be done prior to attempted closed reduction (see footnote to *PRACTICE GUIDELINE 28-8*)
   A. in intact patients, to R/O a condition that might cause worsening of neurologic condition with reduction (e.g. traumatic disc herniation) - must be balanced against risks of transferring patients to MRI
   B. in patients with neurologic deficit (complete or partial SCI)

✖ Contraindications

1. atlatooccipital dislocation (*see page 951*): traction may worsen deficit. If immobilization with tongs/halo is desired, use no more than ≈ 4 lbs
2. types IIA or III hangman's fracture: *see page 960*
3. skull defect/fracture at anticipated pin site: may necessitate alternate pin site
4. use with caution in pediatric age group (do not use if age ≤ 3 yrs)

5. very elderly patients:
6. demineralized skull: some elderly patients, osteogenesis imperfecta…
7. patients with an additional rostral injury
8. patients with movement disorders: constant motion may cause pin erosion through the skull

Application of tongs or halo ring

Supplies: gloves, local anesthetic (typically 1% lidocaine with epinephrine), beta-dine ointment. Optional equipment: razor or hair clipper, scalpel.

Choice of device: a number of cranial "tongs" are available. Crutchfield tongs require predrilling holes in the skull. Gardner-Wells tongs are the most common tongs in use. If later use of halo-vest immobilization is anticipated after acute stabilization, a halo ring may be used with an adapter for the initial cervical traction, and then converted to vest traction at the appropriate time (e.g. post-fusion).

Preparation: placed with patient supine on a gurney or bed. Option: shave hair around proposed pin sites (*see below*). Betadine skin prep, then infiltrate local anesthetic. Option: incise skin with scalpel (prevents pins from driving in surface contaminants).

Gardner-Wells tongs: Pin sites: the pins are placed in the temporal ridge (above the temporalis muscle), **2-3 finger-breadths (3-4 cm) above pinna**. Place directly above external acoustic meatus for neutral position traction; 2-3 cm posterior for flexion (e.g. for locked facets); 2-3 cm anterior for extension. One pin has a central spring-loaded force-indicator. Tighten pins until the indicator protrudes 1 mm beyond the flat surface. Retighten the pins daily until indicator protrudes 1 mm for 3 days only, then stop.

Halo ring: Supplies (in addition to above): optional paddle AKA "spoon" to support the head beyond the edge of the bed. Read all of this (including pointers) before starting

1. ring size: choose an appropriately sized ring that leaves a ≈ 1-2 cm gap between the scalp and the ring all the way around
2. ring position: generally placed at or just below the widest portion of the skull (the "equator"), but the front should be ≈ 1 cm above the orbital rim and the back should be ≈ 1 cm above the pinna[62]. The ring is usually stabilized with temporary pins that have plastic discs where they contact the skull

3. pin sites: choose the threaded holes in the ring that place the pins as perpendicular to the skull as possible as follows
   A. anterior pins: above the lateral two thirds of the orbit
   B. posterior pins: just behind the ears
   C. in pediatrics, additional pins may be placed to further distribute the load on the thinner skull
4. pin insertion: the pins are gradually brought close to the scalp which is then anesthetized with local anesthetic. Pins are then sequentially tightened, starting with any pin then going to the kitty-corner pin, then a third pin and finally its opposite. Most halos provide some type of torque wrench to permit approximately **8 in-lb** of torque for most adults; **2-5 in-lb** for peds
5. placement pointers
   A. the cervical collar is left in place until traction/immobilization is established
   B. try to place the halo as level from left to right as possible. While a skewed placement can be compensated for when attaching the vest, it looks bad
   C. prior to penetrating the forehead skin for anterior pins, have the patient close their eyes and hold them closed as the pins are advanced (this avoids "pinning the eyes open")
   D. avoid placing pins in the temporalis muscle or the temporal squamosa
   E. do not place pins above the medial third of the orbit to avoid the supraorbital and supratrochlear nerves, and to reduce theorist of penetrating the relatively thin anterior wall of the frontal sinus

Post-placement care: For traction, transfer to a bed with ortho headboard with tongs or halo ring in place. Tie a rope to tongs/halo and feed through a pulley at the head of bed. Slight flexion or extension is achieved by changing the height of the pulley relative to the patients long axis.

X-rays: lateral C-spine x-rays immediately after application of traction and at regular intervals and after every change in weights and every move from bed. Check alignment and rule-out overdistraction at any level and atlanto-occipital dislocation (BDI should be ≤ 12 mm, *see page 953*).

Weight: if there is no malalignment and traction is being used just to stabilize the injury and to compensate for ligamentous instability, use 5 lbs for the upper C-spine or 10 lbs for lower levels. To reduce locked facets, *see page 973*. May remove cervical collar once patient is in traction with adequate

reduction or stabilization.

Pin tightening: pins are retorqued in 24 hours. Some authors do one additional tightening the day after that. Avoid further tightenings which can penetrate the skull

Pin care: clean (e.g. half strength hydrogen peroxide), then apply povidone-iodine ointment. Frequency: in hospital: q shift. At home following discharge: twice daily.

Alternatively, simple cleaning with soap and water twice daily is acceptable.

Application of halo vest

For vest placement (i.e. patients not remaining in traction) once the halo ring is placed (*see above*) it needs to be attached to the vest by posts. The mechanism varies between manufacturers. If possible, have the patient in a cotton T-shirt prior to placing the vest (this may require cutting the neck opening to accommodate the ring).

The vest should be snug, but too tight so as to restrict respirations. Shoulder straps should be contacting the shoulders (the vest will tend to ride up when the patient is sitting). Most vests come with a wrench that is taped to the vest for emergency removal.

Reduction of locked facets

See page 973.

Complications

1. skull penetration by pins. May be due to:
   A. pins torqued too tightly
   B. pins placed over thin bone: temporal squamosa or over frontal sinus
   C. elderly patients, pediatric patients, or those with an osteoporotic skull
   D. invasion of bone with tumor: e.g. multiple myeloma
   E. fracture at pin site
2. reduction of cervical dislocations may be associated with neurologic deterioration which is usually due to retropulsed disc[63] and requires immediate investigation with MRI or myelogram/CT
3. overdistraction from excessive weight (especially with upper cervical spine injuries), may also endanger supporting tissues
4. caution with C1-C3 injury, especially with posterior element fracture

(traction may pull fragments in towards canal)

5. infection:
   A. osteomyelitis in pin sites: risk is reduced with good pin care
   B. subdural empyema: rare[64, 65] (*see page 356*)

INDICATIONS FOR EMERGENCY DECOMPRESSIVE SURGERY

Caution: laminectomy in the face of acute spinal cord injury has been associated with neurologic deterioration in some cases. When emergency decompression is indicated, it is usually combined with a stabilization procedure.

Modified recommendations of Schneider[66]

In patients with complete spinal cord lesions, no study has demonstrated improvement in neurologic outcome with either open decompression or closed reduction[67]. In general, surgery is reserved for incomplete lesions (possibly excluding central cord syndrome, *see page 948*) with extrinsic compression, who, following maximal possible reduction of subluxation show:

1. progression of neurologic signs
2. complete subarachnoid block by Queckenstedt test or radiographically (on myelography or MRI)
3. myelogram, CT, or MRI shows bone fragments or soft tissue elements (e.g. hematoma) in the spinal canal causing spinal cord compression
4. necessity for decompression of a vital cervical root
5. compound fracture or penetrating trauma of the spine
6. acute anterior spinal cord syndrome (*see page 950*)
7. non-reducible fracture-dislocations from locked facets causing spinal cord compression

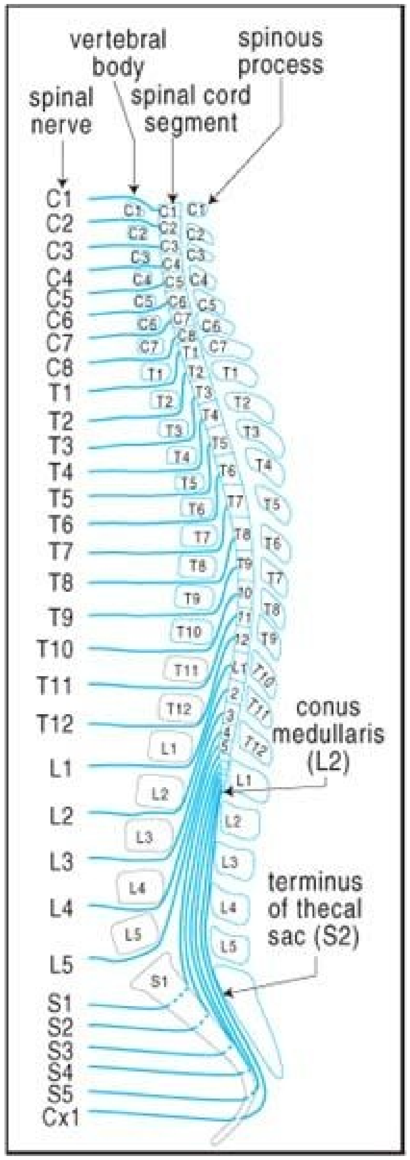


Figure 28-1 Relationship between spinal cord, nerve roots, and bony spine

<u>Contraindications</u> to emergent operation

1. <u>complete</u> spinal cord injury ≥ 24 hrs (no motor or sensory function below level of lesion)
2. medically unstable patient
3. central cord syndrome (controversial, *see page 948*)

28.4. Neurological assessment

Evaluation of the level of the lesion requires familiarity with the following concepts about the relationship between the bony spinal canal and the spinal cord and nerves (*see Figure 28-1*).

1. since there are 8 pairs of cervical nerves and only 7 cervical vertebra
   A. cervical nerves 1 through 8 exit above the pedicles of their like-numbered vertebra
   B. thoracic, lumbar and sacral nerves exit below the pedicles of their like-numbered vertebra
2. due to disproportionately greater growth of the spinal column than the spinal cord during development, the following relationships of the spinal cord to the vertebral column exist:
   A. to determine which segment of the cord underlies a given vertebra:
      1. from T2 through T10: add 2 to the number of the spinous process
      2. for T**11**, T12 and L1, remember that these overlie the **11** lowest spinal segments (L1 through L5, S1 through S5, and Coccygeal-1)
   B. the conus medullaris in the adult lies at about L1 or L2 of the spine

MOTOR LEVEL ASSESSMENT

The following tables are for rapid assessment (see *Table 24-4*, page 787 and *Table 24-6*, page 788 for detailed tables of motor innervation).

Table 28-8 Key muscles for motor level classification
(EXTREMITIES)

RIGHT grade	Segment	Muscle	Action to test	LEFT grade
0-5	C5	biceps	flex elbow	0-5
0-5	C6	wrist extensors	cock up wrist	0-5
0-5	C7	triceps	extend elbow	0-5
0-5	C8	flexor digitorum profundus	flex middle distal phalanx	0-5
0-5	T1	hand intrinsics	abduct little finger	0-5
0-5	L2	iliopsoas	flex hip	0-5
0-5	L3	quadriceps	straighten knee	0-5
0-5	L4	tibialis anterior	dorsiflex foot	0-5
0-5	L5	EHL	dorsiflex big toe	0-5
0-5	S1	gastrocnemius	plantarflex foot	0-5
50	← TOTAL POSSIBLE POINTS →			50
GRAND TOTAL: 100				

ASIA *(American Spinal Injury Association)* MOTOR SCORING SYSTEM

A system[68, 69] that may be rapidly applied to grade 10 key motor segments using the MRC Grading Scale (*Table 24-1*, page 786) from 0-5 on the left and the right, for a total score of 100 possible points (*see Table 28-8*). NB: most muscles receive innervation from two adjacent spinal levels, the levels listed in *Table 28-8* are the lower of the two. The standard considers a segment intact if the motor grade is fair (≥ 3). For additional information, see www.asia-spinalinjury.org.

Table 28-9 Axial muscle evaluation[70]

Level	Muscle	Action to test
C4	diaphragm	tidal volume (TV), FEV_1, and vital capacity (VC)
T2-9 T9-10 T11-12	intercostals upper abdominals lower abdominals	use sensory level, abdominal reflexes, & Beevor's sign (*see below*)

MORE DETAILED MOTOR EVALUATION

Table 28-10 Skeletal muscles and their major spinal innervation
(major contributing segment is shown in boldface)

Segment	Muscle	Action to test	Reflex
C1-4	neck muscles		
C3, 4, 5	diaphragm	inspiration, TV, FEV_1, VC	
C5, 6	deltoid	abduct arm > 90°	
C5, 6	biceps	elbow flexion	biceps
C6, 7	extensor carpi radialis	wrist extension	supinator
C7, 8	triceps, extensor digitorum	elbow and finger extension	triceps
C8, T1	flexor digitorum profundus	grasp (flex distal phalanges)	

C8, T1	hand intrinsics	abduct little finger, adduct thumb	
T2-9	intercostals*		
T9,10	upper abdominals*	Beevor's sign†	abdominal cutaneous reflex‡
T11,12	lower abdominals*		
L2, 3	iliopsoas, adductors	hip flexion	cremasteric reflex§
L3, 4	quadriceps	knee extension	infrapatellar (knee jerk)
L4, 5	medial hamstrings, tibialis anterior	ankle dorsiflexion	medial hamstrings
L5, S1	lateral hamstrings, posterior tibialis, peroneals	knee flexion	
L5, S1	extensor digitorum, EHL	great toe extension	
S1, 2	gastrocs, soleus	ankle plantarflexion	achilles (ankle jerk)
S2, 3	flex digitorum, flex hallucis		
S2, 3, 4	bladder, lower bowel, anal sphincter	clamp down during rectal exam	anal cutaneous reflexΔ, bulbocavernosus & priapism

* also use sensory level to help evaluate these segments

† **Beevor's sign**: used to assess abdominal musculature for level of lesion. Patient lifts head off of bed by flexing neck; if lower abdominal muscles (below ~ T9) are weaker than upper abdominal musculature, then umbilicus moves cephalad. Not helpful if both upper and lower abdominals are weak

‡ the **abdominal cutaneous reflex**: scratching one quadrant of abdomen with sharp object causes contraction of underlying abdominal musculature, causing umbilicus to migrate toward that quadrant. Upper abdominal reflex: T8-9. Lower abdominal reflex: T10-12. This is a cortical reflex (i.e. reflex loop ascends to cortex, and then descends to abdominal muscles). The presence of this response indicates an incomplete lesion for cord injuries above the lower thoracic level

§ **cremasteric reflex**: L1-2 superficial reflex

Δ **anal-cutaneous reflex**: AKA anal wink. Normal reflex: mild noxious stimulus (e.g. pinprick) applied to skin in region of anus results in involuntary anal contraction.

bulbocavernosus (BC) reflex: contraction of anal sphincter in response to pinching penile shaft, or in response to tug on Foley catheter is normal (must be differentiated from the movement of the catheter balloon). Presence of BC reflex used to be taken as an indication of an incomplete injury, but its presence alone is no longer considered to have a good prognosis for recovery.

priapism: in presence of spine trauma, indicates injury to spinal cord resulting in loss of sympathetic tone → dominance of parasympathetic tone. A poor prognosticator for return of function

SENSORY LEVEL ASSESSMENT (DERMATOMES & SENSORY NERVES)

ASIA standards[68]

28 key points identified in *Table 28-12* are scored separately for pinprick and light touch on the left & right side using the grading scale shown in *Table 28-11*, for a maximum possible total of 112 points for pinprick (left & right) and 112 points for light touch (left & right).

NB: regarding the “C4 cape” AKA “bib” region across the upper chest and back: sensory segments “jump” from C4 to T2 with the intervening levels distributed exclusively on the UEs (see *Figure 5-13*, page 94). The location of transition is inconstant from person to person.

RECTAL EXAM

1. external anal sphincter is tested by insertion of the examiner's finger
   A. perceived sensation is recorded as present or absent. Any sensation felt by the patient indicates that the injury is sensory incomplete
   B. note resting sphincter tone and any voluntary sphincter contraction
2. bulbocavernosus reflex **(BC)**: *see footnote, page 946*

Table 28-11 Sensory grading scale

Grade	Description
0	absent
1	impaired (partial or altered appreciation)
2	normal
NT	not testable

Table 28-12 Key sensory landmarks

Level	Dermatome
C2	occipital protuberance
C3	supraclavicular fossa
C4	top of acromioclavicular joint
C5	Lateral side of antecubital fossa
C6	thumb, dorsal surface, proximal phalanx
C7	middle finger, dorsal surface, proximal phalanx
C8	little finger, dorsal surface, proximal phalanx
T1	medial (ulnar) side of antecubital fossa
T2	apex of axilla
T3	third intercostal space **(IS)**
T4	fourth IS (nipple line)
T5	fifth IS (midway between T6 & T8)
T6	sixth IS (xiphoid process)
T7	seventh IS (midway between T6 & T8)
T8	eighth IS (midway between T6 & T10)
T9	ninth IS (midway between T8 & T10)
T10	tenth IS (umbilicus)
T11	eleventh IS (midway between T10 & T12)
T12	inguinal ligament at mid-point

L1	half the distance between T12 & L2
L2	mid-anterior thigh
L3	medial femoral condyle
L4	medial malleolus
L5	dorsum of foot at 3rd MTP joint
S1	lateral heel
S2	popliteal fossa in the mid-line
S3	ischial tuberosity
S4-5	perianal area (taken as 1 level)

ADDITIONAL SENSORY EXAM

The following elements are considered optional but it is recommended that they be graded as absent, impaired or normal:

1. position sense: test index finger and great toe on both sides
2. awareness of deep pressure/deep pain

ASIA IMPAIRMENT SCALE

The ASIA impairment scale*[68] is shown in *Table 28-13* (a modified Frankel Neurological Performance scale[71]).

Table 28-13 ASIA impairment scale

Class	Description
A	**Complete**: no motor or sensory function preserved
B	Incomplete: **sensory** but no motor function preserved below the neurologic level (includes sacral segments S4-5)
C	Incomplete: **motor** function preserved below the neurologic level (more than half of key muscles below the neurologic level have a muscle strength **grade < 3**)*
D	Incomplete: **motor** function preserved below the neurologic level (more than half of key muscles below the neurologic level have a muscle strength **grade ≥ 3**)
E	**Normal**: Sensory & motor function normal

* for muscle strength grading see *Table 24-1*, page 786

* NB: this scale indicates the completeness of spinal cord injury and is separate from the other ASIA

grading scales that appear earlier in this chapter.

28.5. Spinal cord injuries

28.5.1. Complete spinal cord injuries

See *page 930* for definition of complete vs. incomplete spinal cord injury.

In addition to loss of voluntary movement, sphincter control and sensation below the level of the injury, there may be priapism. Hypotension and bradycardia (spinal shock, *see page 930*) may also present.

BULBAR-CERVICAL DISSOCIATION

Occurs as a result of spinal cord injury at or above ≈ C3 (includes SCI from atlanto-occipital and atlantoaxial dislocation). Bulbar-cervical dissociation produces immediate pulmonary and, often, cardiac arrest. Death results if CPR is not instituted within minutes. Patients are usually quadriplegic and ventilator dependent (phrenic nerve stimulation may eventually allow independence from ventilator).

28.5.2. Incomplete spinal cord injuries

CENTRAL CORD SYNDROME

Key concepts:

- disproportionately greater motor deficit in the upper extremities than lower
- usually results from hyperextension injury in the presence of osteophytic spurs
- surgery is often employed for ongoing compression, usually on a non-emergency basis except for rare cases of <u>progressive</u> deterioration

Central cord syndrome **(CCS)** is the most common type of incomplete spinal cord injury syndrome. Usually seen following acute hyperextension injury in an older patient with pre-existing acquired stenosis as a result of bony hypertrophy (anterior spurs) and infolding of redundant ligamentum flavum (posteriorly),

sometimes superimposed on congenital spinal stenosis. Translational movement of one vertebra on another may also contribute. A blow to the upper face or forehead is often disclosed on history, or is suggested on exam (e.g. lacerations or abrasions to face and/or forehead). This often occurs in relation to a motor vehicle accident or to a forward fall, often while intoxicated. Younger patients may also sustain CCS in sporting injuries (see *burning hands syndrome,* page 980). CCS may occur with or without cervical fracture or dislocation[72]. CCS may be associated with acute traumatic cervical disc herniation. CCS may also occur in rheumatoid arthritis.

Pathomechanics

Theory: the centermost region of the spinal cord is a vascular watershed zone which renders it more susceptible to injury from edema. Long tract fibers passing through the cervical spinal cord are somatotopically organized such that cervical fibers are located more medially than the fibers serving the lower extremities (see *Figure 5-12*, page 93).

Presentation[73]

The clinical syndrome is somewhat similar to that seen in syringomyelia.

1. motor: weakness of upper extremities with lesser effect on lower extremities
2. sensory: varying degrees of disturbance below level of lesion may occur
3. myelopathic findings: sphincter dysfunction (usually urinary retention)

Hyperpathia to noxious and non-noxious stimuli is also common, especially in the proximal portions of the upper extremities, and is often delayed in onset and extremely distressing to the patient[74]. Lhermitte’s sign occurs in ≈ 7% of cases.

Natural history

There is often an initial phase of improvement (characteristically: LEs recover first, bladder function next, UE strength then returns with finger movements last; sensory recovery has no pattern) followed by a plateau phase and then late deterioration[75]. 90% of patients are able to walk with assistance within 5 days[76]. Recovery is usually incomplete, and the amount of recovery is related to the severity of the injury and patient age[77].

If CCS results from hematomyelia with cord destruction (instead of cord contusion), then there may be extension (upward or downward).

Evaluation

Findings: young patients tend to have disc protrusion, subluxation, dislocation or fractures[76]. Older patients tend to have multi-segmental canal narrowing due to osteophytic bars, discs, and inbuckling of ligamentum flavum[76].

C-spine x-rays: may demonstrate congenital narrowing, superimposed osteophytic spurs, traumatic fracture/dislocation. Occasionally, AP narrowing alone without spurs may be seen[72]. Plain x-rays will fail to demonstrate canal narrowing due to: thickening or inbuckling of ligamentum flavum, hypertrophy of facet joints, and poorly calcified spurs[72].

Cervical CT scan: also helpful in diagnosing fractures and osteophytic spurs. Not as good as MRI for assessing status of discs, spinal cord and nerves.

MRI: discloses compromise of anterior spinal canal by discs or osteophytes (when combined with plain C-spine x-rays, it increases the ability to differentiate osteophyte from traumatic disc herniation). Also good for evaluating ligamentum flavum. T2WI may show spinal cord edema acutely[78], and can detect hematomyelia. MRI is poor for identifying fractures.

Treatment

PRACTICE GUIDELINE 28-9 ACUTE CENTRAL CORD INJURIES

Level III[77]

- because of possible cardiac, pulmonary & BP disturbances, *many** of these patients *may* require management in an ICU or other monitored setting (for cardiac, hemodynamic & respiratory monitoring), *especially* patients with severe neurologic deficits
- maintain MAP 85-90 mm Hg (use BP augmentation if necessary) for the 1st week after injury to improve spinal cord perfusion
- early reduction of fracture-dislocation injuries is recommended
- surgical decompression, particularly for focal and anterior spinal cord compression that is approached anteriorly, *seems** to be of benefit in *selected* patients

* all italics added by the editor

The indications, timing and best treatment method for CCS remains

controversial. Initial management options include the methylprednisolone spinal-cord injury protocol for patients seen within 8 hours of the time of injury (*see page 936*).

Indications for surgery:

1. continued compression of the spinal cord[79 (p 1010)] that correlates with the level of deficit with any of the following:
   A. persistent significant motor deficit following a varying period of recovery (see *Timing of surgery* below)
   B. deterioration of function
   C. continued significant dysesthetic pain
2. instability of the spine

Improvement has been shown in short and long-term follow-up with subacute decompression of the offending lesion[76]. Nonsurgical treatment results in a longer period of pain and weakness in many cases.

Timing of surgery: A perennial point of controversy. Classic teaching was that *early* surgery for this condition is <u>contraindicated</u> because this may worsen the deficit. In the absence of spinal instability, traditional management consisted of bed rest in a soft collar for ≈ 3-4 weeks, with consideration for surgery after this time, or else gradual mobilization in the same collar for an additional 6 weeks. It is presently felt that there is no solid evidence that *early* decompressive surgery (without cord manipulation) is actually harmful, but there is also no evidence that it is helpful, either. There may be good justification for *early* surgery in the rare patient who is improving and then deteriorates[80], however, great restraint must be used in avoiding what would be an inappropriate operation in many patients[81]. Surgery may improve the rate and degree of recovery in selected patients[82]. Surgery has been recommended for patients with gross spinal instability or for patients with significant persistent cord compression (e.g. by osteophytic spurs) who fail to progress consistently after an initial period of improvement[78], often within 2-3 weeks following the trauma. Better results occur with decompression within the first few weeks or months rather than very late (e.g. ≥ 1-2 years)[79 (p 1010)].

Σ There is no role for surgery without ongoing compression or instability. The rare patient with ongoing compression undergoing documented <u>progressive deterioration</u> should be decompressed ASAP. Improving patients should be followed and decompression can be done electively for ongoing compression. There is controversy regarding timing of surgery for stable CCS and ongoing compression: while Class I or II data are lacking, there seems to be a trend to decompress these patients as soon as they are medically stable without an arbitrary waiting period.

Technical considerations: The most rapid procedure to decompress the cord is often a multi-level laminectomy. This is frequently accompanied by dorsal migration of the spinal cord which may be seen on MRI[75]. With myelopathy, fused patients fare better than those that are just decompressed without fusion. Fusion may be accomplished posteriorly (e.g. with lateral mass screws and rods) at the time of decompression, or anteriorly (e.g. multi-level discectomy, or corpectomy with strut graft and anterior cervical plating) at the same sitting as the laminectomy or staged at a later date.

Prognosis

In patients with cord contusion without hematomyelia, ≈ 50% will recover enough LE strength and sensation to ambulate independently, although typically with signifi-cant spasticity. Recovery of UE function is usually not as good, and fine motor control is usually poor. Bowel and bladder control often recovers. Elderly patients with this condition generally do not fare as well as younger patients, with or without surgical treatment (only 41% over age 50 become ambulatory, versus 97% for younger patients[83]).

Anterior Cord Syndrome

AKA anterior spinal artery syndrome. Cord infarction in the territory supplied by the anterior spinal artery. Some say this is more common than central cord syndrome.

May result from occlusion of the anterior spinal artery, or from anterior cord compression, e.g. by dislocated bone fragment, or by traumatic herniated disc.

Presentation

1. paraplegia, or (if higher than ≈ C7) quadriplegia
2. **dissociated sensory loss** below lesion:
   A. loss of pain and temperature sensation (spinothalamic tract lesion)
   B. preserved two-point discrimination, joint position sense, deep pressure sensation (posterior column function)[84]

Evaluation

It is vital to differentiate a non-surgical condition (e.g. anterior spinal artery occlusion) from a surgical one (e.g. anterior bone fragment). This requires one or more of: myelography, CT, or MRI.

Prognosis

The worst prognosis of the incomplete injuries. Only ≈ 10-20% recover functional motor control. Sensation may return enough to help prevent injuries (burns, decubitus ulcers…).

BROWN-SÉQUARD SYNDROME

Spinal cord hemisection. First described in 1849 by Brown-Sequard[85].

Classical findings (rarely found in this pure form):

- ipsilateral findings:
  - motor paralysis (due to corticospinal tract lesion) below lesion
  - loss of posterior column function (proprioception & vibratory sense)
- contralateral findings: **dissociated sensory loss**
  - loss of pain and temperature sensation inferior to lesion beginning 1-2 segments below (spinothalamic tract lesion)
  - preserved light (crude) touch due to redundant ipsilateral and contralateral paths (anterior spinothalamic tracts)

Etiologies

Usually a result of penetrating trauma, it is seen in 2-4% of traumatic spinal cord injuries[86]. Also may occur with radiation myelopathy, cord compression by spinal epidural hematoma, large cervical disc herniation[87-89] (rare), spinal cord tumors, spinal AVMs, cervical spondylosis, and spinal cord herniation (*see page 514*).

Prognosis

This syndrome has the best prognosis of any of the incomplete spinal cord injuries. ≈ 90% of patients with this condition will regain the ability to ambulate independently as well as anal and urinary sphincter control.

POSTERIOR CORD SYNDROME

AKA contusio cervicalis posterior. Relatively rare. Produces pain and paresthesias (often with a burning quality) in the neck, upper arms, and torso. There may be mild paresis of the UEs. Long tract findings are minimal.

28.6. Cervical spine fractures

Also see *C-Spine*, page 135 for cervical x-rays. One system of classifying cervical spine fractures identifies the following subatlantal injuries[90] (*see below* for occiptoatlantoaxial injuries, *see page 955* for atlantoaxial subluxation/dislocation):

1. hyperextension fracture-dislocations
   A. posterior fracture-dislocation of the dens
   B. traumatic spondylolisthesis of the axis (hangman's fracture, *see page 959*)
   C. hyperextension sprain (momentary dislocation) with fracture
   D. hyperextension fracture-dislocation with fractured articular pillar
   E. hyperextension fracture-dislocation with comminution of the vertebral arch
2. hyperflexion fracture-dislocations
   A. anterior fracture-dislocation of the dens (*see page 963*)
   B. hyperflexion sprain: rare. Occurs when posterior ligaments are disrupted but locking of articular facets does not occur (*see page 971*)
   C. locked articular facets with fracture (*see page 972*)
   D. "teardrop" fracture-dislocation (*see page 970*)

28.6.1. Occiptoatlantoaxial injuries

28.6.1.1. Atlanto-occipital dislocation

See *Occiptoatlantoaxial-complex anatomy* on page 91 for relevant anatomy.

Atlanto-occipital dislocation **(AOD)** AKA craniocervical junction dislocation. Disruption of the stability of the craniocervical junction (which results from ligamentous injuries). Probably underdiagnosed, may be present in ≈ 1% of patients with "cervical spine injuries"[91] (definition of cervical spine injuries not specified), found in 8-19% of fatal cervical spine injury autopsies[92, 93]. More than twice as common in pediatrics as adults, possibly owing to the flatter (i.e. less cupped) condyles in peds, the higher ratio of cranium to body weight, and increased ligamentous laxity. Patients usually either have minimal neurological deficit or exhibit bulbar-cervical dissociation **(BCD)** (*see page*

948). Some may exhibit cruciate paralysis (*see page 1196*). Most mortality results from anoxia due to respiratory arrest as a result of BCD.

Classification[94]

For classification, *see Figure 28-2*. Combinations (e.g. anterior-distracted AOD[95]) may also occur.

Type I anterior dislocation of occiput relative to the atlas

Type II longitudinal dislocation (distraction)

Type III posterior dislocation of occiput

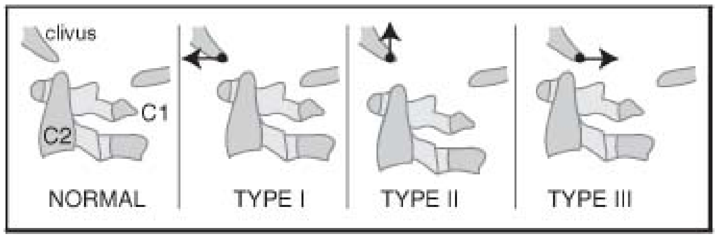


Figure 28-2 Classification of atlanto-occipital dislocation

PRACTICE GUIDELINE 28-10 ATLANTOOCCIPITAL DISLOCATION INJURIES

Diagnosis

Level III[96]

- lateral C-spine x-ray
- if it is desired to employ a radiologic method of measurement, the BAIBDI method (*see page 953*) is recommended
- upper cervical prevertebral soft-tissue swelling on an otherwise nondiagnostic plain lateral C-spine x-ray should prompt additional imaging
- if there is clinical suspicion of AOD, and plain x-rays are nondiagnostic, CT or MRI is recommended, especially for non-Type II dislocations

Treatment

Level III[96]

- internal fixation & arthrodesis using one of a variety of methods
- ✖ CAUTION: traction may be used in the management of AOD, but it is associated with a 10% risk of neurologic deterioration

Clinical presentation

1. may be neurologically intact, therefore must be ruled-out in any major trauma
2. bulbar-cervical dissociation: *see page 948*
3. may have lower cranial nerve deficits (as well as VI palsies) ± cervical cord injury
4. worsening neurologic deficit with the application of cervical traction: check lateral C-spine films immediately after applying traction (*see page 943*)

Radiographic evaluation

Numerous methodologies have been devised to radiographically diagnose AOD. Most utilize surrogate markers for the end-point of interest: instability of the occipitalcervical junction. None are completely reliable[97]. Measurements on CT scans are more accurate than plain radiographs (landmarks are easier to identify, no magnification or rotation error…) - however, normal values may differ from plain radiographs. Some methods are shown in *Table 28-15* (recommended: BAI-BDI method & the AOI method).

Technical suggestions

1. radiographs: verify that the film is a true lateral (e.g. check alignment of the two mandibular rami as well as of the posterior clinoids)
2. CT: sensitivity, specificity, and positive/negative predictive values of most of the these measures improves when applied to sagittal CT reconstructions[98] (relevant landmarks could be identified in > 99% of CTs, vs. 39-84% on x-ray)

Powers' ratio[91]: distance **BC** (basion to posterior arch of atlas) is divided by distance **AO** (opisthion to anterior arch of atlas), *see Table 28-15*. Interpretation is shown in *Table 28-14*.

✖ Cannot be used with any fracture involving the atlas or the foramen magnum, or with congenital anatomic abnormalities. Applies only to anterior AOD (i.e. not for posterior or distracted AOD).

Table 28-14 Powers' ratio

Ratio BC/AO	Interpretation	Comment

< 0.9	normal	1 standard deviation below the lowest case of AOD
≥ 0.9 and < 1	"grey zone" (indeterminate)	included 7% of normals and no cases of AOD
≥ 1	AOD	encompassed all AOD cases

* original study of lateral x-ray in a supine patient with a target-film distance of 40 in. (1 m). The sensitivity of the BAI-BDI method for AOD is good when all landmarks can be identified, but still may only be ≈ 75%[99]

† for this study, peds is defined up to the age of 10 years, by age ≈ 8-10 years the C-Spine reaches adult proportions (not necessarily size)

‡ os = ossiculum terminale (see page 966)

§ the articular process of C1 is often obscured by the tip of the mastoid process on plain films

Δ the opisthion cannot be identified in ≈ 56% of lateral C-spine x-rays[100]

¶ could not be measured in many peds cases often due to lack of ossification (usually of posterior C1 arch)

A helpful rule-of-thumb: the inferior tip of the clivus should point directly to tip of dens (this may be obscured on x-ray).

Additional CT clues: there may be blood in the basal cisterns (an indirect sign). On thin-cut axial CT, there may be one or more slices showing no bone (abnormal).

Management

Initial management: If AOD is suspected, immediately immobilize the neck with halo orthosis or with sandbags. ✖ Do not apply cervical traction in an attempt to reduce AOD because of risk of neurologic deterioration (option: 2-4 lbs may be used early only for immobilization in adults, not for reduction).

Subsequent management: Controversial whether operative fusion vs. prolonged immobilization (4-12 months) with halo brace is required. However, posterior occipito-cervical fusion is usually recommended (see *atlantooccipital dislocation injuries*, page 952). Horn et al.[99] suggest that patients be grouped and then managed as shown in *Table 28-16*.

In infants: reduce in the OR and fuse (usually with transarticular screws).

Table 28-16 Grading & management of AOD[99]

Grade	Definition	Management
I	no abnormal CT criteria* with only moderately abnormal MRI (high signal in posterior ligaments or occipoatlantal joints)	external orthosis (halo or collar)
II	≥ 1 abnormal CT criteria* or grossly abnormal MRI findings in occipoatlantal joints, tectorial membrane, or alar or cruciate ligaments	surgical stabilization

* CT criteria used: Power's ratio, BAI-BDI, X-line

Prognosis

The most important predictor of outcome is the severity of neurologic injuries at the time of presentation[99]. Among AOD patients who survived the initial injury, those with severe TBI and brainstem dysfunction or complete

bulbar-cervical dissociation all had poor outcome[99]. Those with incomplete SCI or nonsevere TBI may improve.

28.6.1.2. Occipital condyle fractures

Key concepts:

- uncommon (0.4% of trauma patients)
- may present with lower cranial nerve deficits which may be delayed in onset (e.g. hypoglossal nerve palsy), mono-, para-, or quadriparesis or plegia
- W/U: ✔ CT scan with reconstructions (rarely detected on plain x-rays)
- Tx: usually treated with rigid collar. Indications for occipitocervical fusion or halo immobilization: craniocervical misalignment (occipital-C1 interval > 2.0 mm)

PRACTICE GUIDELINE 28-11 OCCIPITAL CONDYLE FRACTURES

Diagnosis

Level II[114]

- clinical suspicion should be raised by the presence of ≥ 1 of the following: blunt trauma with high-energy craniocervical injuries, altered consciousness, occipital pain or tenderness, impaired cervical movement, lower cranial nerve palsies, or retropharyngeal soft-tissue swelling
- CT* is recommended for establishing the diagnosis

Level III[114]: MRI is recommended to assess the integrity of the craniocervical ligaments

Treatment

Level III[114]: external cervical immobilization†

* with reconstructions

† Maserati et al.[110] recommend occipitocervical fusion for craniocervical misalignment (retrospective review)

Rare. Incidence: 0.4% (in a series of 24,745 consecutive trauma patients surviving to the E/R110). Occipital condyle fractures **(OCF)** were first described in 1817 by Bell[111].

Classification:

A widely used system is that of Anderson & Montesano[113] which is shown in *Table 28-17*.

Maserati et al.[110] classified patients simply on the basis of whether craniocervical misalignment was present or absent on CT with reconstructions (craniocervical misalignment (they defined as an occipital condyle-C1 interval > 2.0 mm). They felt other classification systems were superfluous as they did not affect outcome in their retrospective review (see *Treatment* below).

Table 28-17 Anderson & Montesano classification of occipital condyle fractures

Type	Description
I	comminuted from impact: may occur from axial loading
II	extension of linear basilar skull fracture[112]
III	avulsion of condyle fragment (traction injury): may occur during rotation, lateral bending, or a combination of mechanisms. Considered unstable by many

Treatment

Controversial. Lower cranial nerve deficits often develop in untreated cases of OCF, and may resolve or improve with external immobilization. Anderson & Montesano Types I & II have been treated with or without external immobilization (cervical collar or, occasionally, halo) without obvious difference. External immobilization **x** 6-8 weeks is suggested for Type III fractures because of the higher risk of delayed deficits.

In a retrospective review of 100 patients with OCF[110], 3 patients underwent occipitocervical fusion (*see page 179*) for craniocervical misalignment (2) or unrelated C1-2 fracture (1). The remainder (without craniocervical misalignment) were treated with a rigid collar and delayed clinical & radiographic follow-up. None of their unoperated patients had neurologic deficit, and none developed delayed instability, malalignment, or neurologic deficit (regardless of their classification on the other systems in use).

28.6.2. Atlantoaxial subluxation/dislocation

Lower morbidity and mortality than atlantooccipital dislocation[115]. See *Occiptoatlantoaxial-complex anatomy* on page 91 for relevant anatomy.

Types of atlantoaxial subluxation:

1. rotatory: (*see below*) usually seen in children after a fall or minor trauma
2. anterior: more ominous (*see below*)
3. posterior: rare. Usually from erosion of odontoid. Unstable. Requires fusion

ATLANTOAXIAL ROTATORY SUBLUXATION

Key concepts:

> • typically seen in children
> • associations: trauma, RA, respiratory tract infections in peds (Grisel syndrome)
> • often present with cock-robin head position (tilt, rotation, sl. flexion)
> • classification: Fielding & Hawkins (*Table 28-18*)
> • Tx: early traction often successful. Treat infection in Grisel syndrome. Subluxation unreducible in traction may need transoral release then posterior fusion

Rotational deformity at the atlanto-axial junction is usually of short duration and easily corrected. Rarely, the atlantoaxial joint locks in rotation (AKA atlantoaxial rotatory *fixation*[116]). Usually seen in children. May occur spontaneously (with rheumatoid arthritis[117] or with congenital dens anomalies), following major or minor trauma (including neck manipulation or even with neck rotation while yawning[116]), or with an infection of the head or neck including upper respiratory tract (known as **Grisel syndrome**[118]: inflammation may cause mechanical and chemical injury to the facet capsules and/or transverse atlantal ligament **(TAL)**). The Fielding and Hawkins classification[116] is shown in *Table 28-18*.

The dislocation may be at the occipito-atlantal and/or the atlanto-axial articulations[119]. The mechanism of the irreducibility is poorly understood. With an intact TAL, rotation occurs without anterior displacement. If the TAL is incompetent as a result of trauma or infection, there may also be anterior displacement with more potential for neurologic injury. Posterior displacement occurs only rarely[116].

The vertebral arteries **(VA)** may be compromised in excessive rotation, especially if it is combine with anterior displacement.

Table 28-18 Fielding & Hawkins classification of rotatory atlantoaxial subluxation

Type	Description		AD (mm)	Comment
	TAL*	facet injury		
I	intact	bilateral	≤ 3	dens acts as pivot
II	injured	unilateral	3.1-5	intact joint acts as pivot
III	injured	bilateral	> 5	rare. Very unstable
IV	incompetence of the odontoid with posterior displacement			rare. Very unstable

* TAL = transverse atlantal ligament, AD = anterior displacement of C1 on C2

Clinical findings

Patients are usually young. Neurologic deficit is rare. Findings may include: neck pain, headache, torticollis (characteristic "**cock robin**" head position with ≈ 20° lateral tilt to one side, 20° rotation to the other, and slight (≈ 10°) flexion - *see page 541* for DDx), reduced range of motion, and facial flattening[116]. Although the patient cannot reduce the dislocation, they can increase it with head rotation towards the subluxed joint with potential injury to the high cervical cord.

Brainstem and cerebellar infarction and even death may occur with compromise of circulation through the VAs[120].

Radiographic evaluation

X-rays: Findings (may be confusing) include:

1. pathognomonic finding on AP C-spine x-ray in severe cases: frontal projection of C2 with simultaneous oblique projection of C1[121 (p 124)]. In less severe cases, the C1 lateral mass that is forward appears larger and closer to the midline than the other
2. asymmetry of the atlantoaxial joint that is not correctable with head rotation, which may be demonstrated by persistence of asymmetry on open mouth odontoid views with the head in neutral position and then rotated 10-15° to each side
3. the spinous process of the axis is tilted in one direction and rotated to the other (may occur in torticollis of any etiology)

CT scan: Demonstrates rotation of the atlas[119].

MRI: May assess the competence of the transverse ligament.

Treatment

Grisel's syndrome: appropriate antibiotics for causative pathogen with traction (*see below*) and then immobilization for the subluxation as follows[118]: Fielding (*see Table 28-18*) Type I: soft collar, Type II: Philadelphia collar or SOMI, Type III or IV: halo. After 6-8 weeks of immobilization, check stability with flexion-extension x-rays. Surgical fusion for residual instability

Traction: If treated within the first few months[122] the subluxation can usually be reduced with gentle traction (in children start with 7-8 lbs and gradually increase up to 15 lbs over several days, in adults start with 15 lbs and gradually increase up to 20). If the subluxation is present > 1 month, traction is less successful. Active left-right neck rotation is encouraged in traction.

If reducible, immobilization in traction or halo is maintained **x** 3 months[116] (range: 6-12 weeks).

Surgical fusion: Subluxation that cannot be reduced or that recurs following immobilization should be treated by surgical arthrodesis after 2-3 weeks of traction to obtain maximal reduction. The usual fusion is C1 to C2 (*see page 183*) unless other fractures or conditions are present[116]. Fusion may be performed even if the rotation between C1 & C2 is not completely reduced. For irreducible fixation, a staged procedure can be done with anterior transoral release of the atlantoaxial complex (the exposure is taken laterally to expose the atlantoaxial joints which must be done carefully to avoid injury to the VAs, soft tissue is carefully removed from the joints and the atlantodental interval, no attempt at reduction was made at the time of this 1st stage) followed by gradual skull traction and then a second stage posterior C1-2 fusion[122]

ANTERIOR ATLANTOAXIAL SUBLUXATION[115] (AAS)

One third of patients have neurologic deficit or die. Subluxation may be due to:

1. disruption (rupture) of the transverse (atlantal) ligament **(TAL)**: the atlantodental interval **(ADI)** (*see below*) will be increased
   A. attachment points of the TAL may be weakened in rheumatoid arthritis (*see page 495*)
   B. trauma: may cause anatomic or functional ligament disruption (*see below*)
2. incompetence of the odontoid process: ADI will be normal
   A. odontoid fracture
   B. congenital hypoplasia (e.g. Morquio syndrome, *see page 494*)

Evaluation

Both CT & MRI are recommended to evaluate fractures, TAL & its bony attachments.

Treatment

1. TAL disruption: *see below*
2. odontoid fractures with intact TAL: managed as outlined on *page 964*

TRANSVERSE ATLANTAL LIGAMENT ***(TAL)*** *INJURIES*

For relevant anatomy, see *Occiptoatlantoaxial-complex anatomy* on page 91.

Classification of TAL disruption[123]

Type I: anatomic disruption. Tear of TAL itself. Rare (the odontoid usually fractures before the TAL tears). Unlikely to heal. Requires surgical stabilization

Type II: physiologic disruption. Detachment of the tubercle of C1 to which TAL is attached (see *Figure 5-11*, page 92) as may occur in comminuted C1 lateral mass fractures. 74% chance of healing with immobilization (halo recommended[123])

"V" shaped pre-dens space[124]: Widening of the upper space between the anterior arch of C1 and the odontoid seen on lateral C-spine flexion x-ray. It is not known if this increased mobility represents elongation or laxity of the transverse ligament and/or the posterior ligamentous complex. This may also be a normal finding in flexion in peds.

Assessing the integrity of the transverse ligament

1. disruption of the TAL may be inferred indirectly from
   A. **Rule of Spence**: on open-mouth odontoid x-ray, if the total overhang of both C1 lateral masses on C2 is **≥ 7 mm** (*see page 136* for details)
   B. **atlantodental interval (ADI)**: > 3 mm in adults, > 4 mm in peds (*see page 136* for details)
2. MRI may image TAL directly. Findings of disruption (axial MRI): high signal within TAL on gradient-echo MRI, loss of continuity of TAL, blood at insertion site[125]

3. CT demonstrates bony injuries in regions of TAL insertion on C1 tubercles

Treatment

One approach is to fuse all Type I TAL injuries, and those Type II TAL injuries that are still unstable after 3-4 months of immobilization[123]. Fusion is also recommended with irreducible subluxations. If C1 is intact, a C1-2 fusion is usually adequate. For situations involving C1 fractures, *see below*.

28.6.3. Atlas (C1) fractures

Acute C1 fractures account for 3-13% of cervical spine fractures[126]. 56% of 57 patients had isolated C1 fractures; 44% had combination C1-2 fractures; 9% had additional non-contiguous C-spine fractures. 21% had associated head injuries[126].

ISOLATED C1 (ATLAS) INJURIES

CLASSIFICATION OF C1 FRACTURES[127]

Type I: fractures involving a single arch (31-45% of C1 fractures)

Type II: burst fracture (37-51%): the classic Jefferson fracture (*see below*)

Type III: lateral mass fractures of the atlas (13-37%)

Jefferson fracture

Described by Sir Geoffrey Jefferson[128]. Classically a four-point (burst) fracture of the C1 ring[129], but the term is now often used to include the more common three or two-point fractures[130], the latter through the C1 arches (thinnest portion). Usually from axial load (a “blow-out” fracture). 41% chance of an associated C2 fracture.

In pediatrics, it is critical to differentiate a C1 fracture from the normal synchondroses (*see page 137*), and from pseudospread of the atlas (*see page 933*). A fracture may also occur through the unfused synchondroses.

Unstable, usually no neurologic deficit if isolated (due to large canal diameter at this level, plus tendency for fragments to be forced outwards away from spinal cord).

Stability

To reiterate: stability of the occiptoatlantoaxial complex is primarily due to ligaments, with little contribution from bony articulations (see *Occiptoatlantoaxial-complex anatomy* on page 91). ★ Integrity of transverse ligament **(TAL)** is the most important determinant of stability (see *Assessing the integrity of the transverse ligament* above).

Clinical

Neurologic deficit is rare. 3 of 25 patients with Jefferson fractures sustained neurologic injuries (1 complete injury, 2 central cord syndromes) in one series.

Evaluation

Complete C-spine series and thin section high-resolution CT from C1 through C3 to delineate details of C1 fracture and to assess for associated C2 injury.

MRI to assess TAL.

Treatment

PRACTICE GUIDELINE 28-12 ISOLATED ATLAS FRACTURES

Treatment

Level III[131]: for isolated atlas fractures:

- if the transverse ligament is intact: cervical immobilization alone
- if the transverse ligament is disrupted*: either
  - A. cervical immobilization alone
  - B. or, surgical fixation and fusion

* disruption of the TAL may be anatomic or physiologic (see text for details)

Treatment options depend heavily on status of TAL, and are delineated in *Table 28-19*[131]. When external immobilization is employed, it is used for 8-16 weeks (mean = 12).

Fusion options when surgery is indicated[123]:

1. unilateral ring or anterior C1 arch fractures: C1-2 fusion
2. multiple ring fractures or posterior C1 arch fractures: occipital-cervical fusion

Table 28-19 Treatment options for isolated C1 fractures

Fracture type	Treatment options
anterior or posterior arch	collar or SOMI
anterior AND posterior arch (burst) stable (TAL* intact) unstable (TAL disrupted)	collar or SOMI, halo halo, C1-2 stabilization & fusion
lateral mass fractures comminuted fracture transverse process fracture	collar or SOMI, halo collar or SOMI

* abbreviations: TAL = transverse atlantal ligament

Surgical operations the do not involve arthrodesis include: posterior C1 screw placement, anterior transoral screw/plate placement.

OUTCOME

In many series[126, 132], treatment without surgery results in satisfactory outcome when the TAL is not disrupted.

28.6.4. Axis (C2) fractures

Acute fractures of the axis represent ≈ 20% of cervical spine fractures. Neurological injury is uncommon, and occurs in < 10% of cases. Most injuries may be treated by rigid immobilization.

Steele's rule of thirds: each of the following occupies one third of the area of the canal at the level of the atlas: dens, space, spinal cord[133].

Types of C2 fractures

1. odontoid fractures (*see page 963*): type II is the most common injury of the axis
2. hangman's fracture: *see below*
3. miscellaneous C2 fractures: *see page 967*

28.6.4.1. Hangman's fracture

Key concepts:

> • bilateral fracture through the pars interarticularis of C2 with traumatic subluxation of C2 on C3, most often due to hyperextension + axial

loading
- most are stable with no neurologic deficit
- classification: Levine system (*Table 28-20*). Critical dividing line: disruption of C2-3 disc (Types II and higher) which may render the fracture unstable
- W/U: ✔ cervical CT with sagittal & coronal recons for all. ✔ Cervical MRI to assess C2-3 disc disruption (Levine II). ✔ CTA for dissection if fx passes thru foramen transversarium (consider for all C2 fractures - see *Table 28-36*, page 983)
- most do well with non-halo immobilization **x** 8-14 weeks (exceptions: severe/unstable fractures (*see page 961*) or those that do not remain aligned in brace)

AKA **traumatic spondylolisthesis of the axis**.

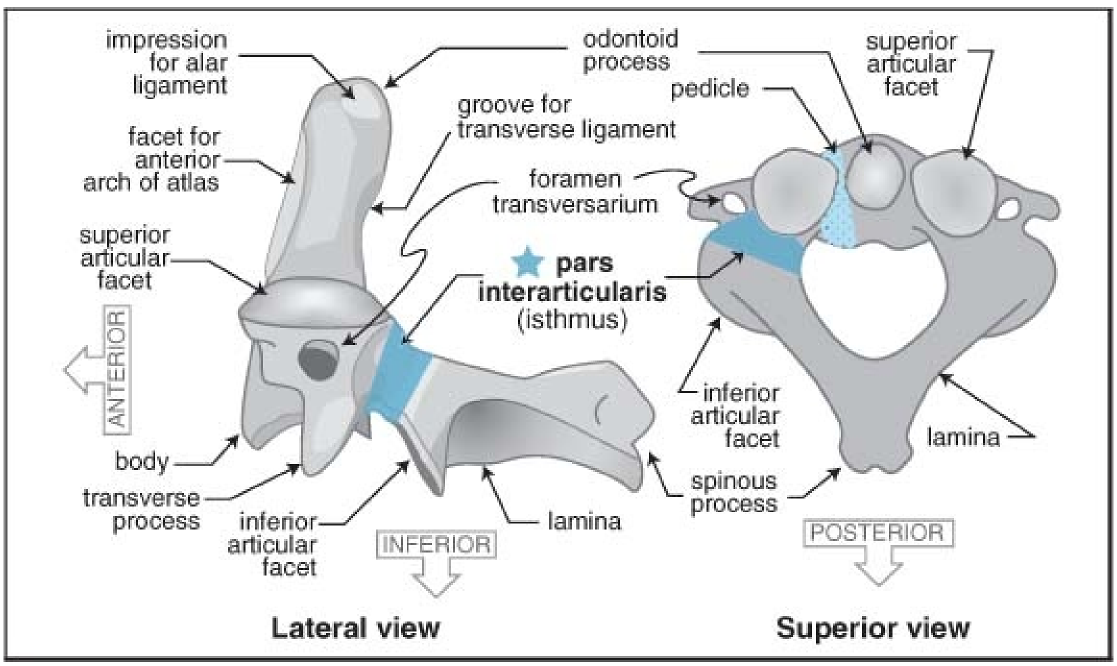


Figure 28-3 Anatomy of axis (C2). The pars interarticularis is shown in dark blue

Description: bilateral fracture through the pars interarticularis (isthmus) of the pedicle[A] of C2 (*see Figure 28-3*). There is often anterior subluxation of C2 on C3.

A. the configuration of C2 is unique, and the distinction between the pars and the pedicle is ambiguous

The term “hangman’s fracture” **(HF)** was coined by Schneider et al.[134] although the mechanism of most modern HFs (hyperextension and axial loading, from MVAs or diving accidents) differs from that sustained in judicial hangings (where submental placement of the knot results in hyperextension and *distraction*[135]). Some cases may be due to forced flexion or compression of the neck in extension.

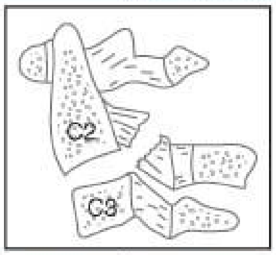
Pediatrics: rare in children < 8 years old where the forces tend to fracture the incompletely fused odontoid (epiphyseal fracture - *see page 137*). In pediatrics, consider pseudosubluxation in the differential diagnosis (*see page 933*).

Usually stable. Deficit is rare. Nonunion is rare. 90% heal with immobilization only. Operative fusion is rarely needed. Fractures of C2 that do not go through the isthmus are not true hangman’s fractures and may require different management (see *Miscellaneous C2 fractures*, page 967).

CLASSIFICATION

Levine/Effendi classification: The system of Effendi et al.[136] as modified by Levine[137] and others (*see Table 28-20*) is widely used in grading adult HF (not applicable to peds). Angulation is measured as the angle between the inferior endplates of C2 and C3. Anterior subluxation of C2 on C3 > 3 mm (Type II) is a surrogate marker for C2-3 disc disruption which can be evaluated more directly with cervical MRI.

Table 28-20 Levine classification of hangman's fractures (modified Effendi system)*

Type	Description	Radiographic Findings	Mechanism	Comment
I	vertical pars fx just posterior to the VB	≤ 3 mm subluxation of C2 on C3 & no angulation	axial loading & extension	stable on flexion/extension x-rays. Neurologic deficit rare
I A	fx lines on each side are not parallel. Fx may pass thru foramen transversarium on one side	fx line may not be visible on x-ray. Anterior C2 VB may be subluxed 2-3 mm anteriorly on C3 & the C2 VB may appear elongated.	may be hyperextension + lateral bending	"atypical hangman's fracture"[139]. Spinal canal may be narrowed. 33% incidence of paralysis
II	vertical fx thru pars. Disruption of C2-3 disc & posterior longitudinal ligament	subluxation of C2 on C3 > 3 mm and/or angulation†. Slight anterior compression of C3 possible	axial loading & extension with rebound flexion	may lead to early instability. Neurologic deficit rare. Usually reduces with traction
IIA	oblique fx (usually anterior-inferior to posterior superior) 	little subluxation (usually ≤ 3 mm) but more angulation (can be > 15°)	flexion distraction (posterior arch fails in tension)	rare (< 10%). Unstable. ✖ Traction → increased angulation & widening of disc space ∴ do not use traction
III	Type II + bilateral C2-3 facet capsule disruption. C2 posterior arch is free floating. Anterior longitudinal ligament may be disrupted or stripped off C3	facets of C2/C3 may be subluxed or locked	unclear, may be flexion (capsule disruption) followed by compression (isthmus fracture)	rare. Neurologic deficit may occur & may be fatal. Facet dislocation usually cannot be reduced by closed reduction. ✖ Traction may be dangerous (*see text*)

* Effendi et al.[136], Levine and Edwards[137], Sonntag and Dickman[115] and Levine[138]

† amount of angulation was not specified in original article, but > 10° has been suggested by some

Grading system of Frances et al: The grading system[140] is shown in *Table 28-21*. The methodology of measurements is depicted in *Figure 28-4*.

Levine/Francis correlation: In a series of 340 axis fractures[141], the most common fracture type was Type I in the Levine system (72%) and Grade I in the Francis system (65%); and there was a close correlation as follows:

Levine Type I ≈ Francis Grade I

Levine Type III ≈ Francis Grade IV

Other fracture types: Not all fractures fit into one or both of these classification systems[142]. Example: coronally oriented fracture extending through the posterior C2 vertebral body.

Table 28-21 Francis Grading* system for hangman's fracture

Grade	Angulation θ	Displacement

I	< 11°	d < 3.5 mm
II	> 11°	
III	< 11°	d > 3.5 mm and d/b < 0.5
IV	> 11°	
V		disc disruption

* *see Figure 28-4* for definitions

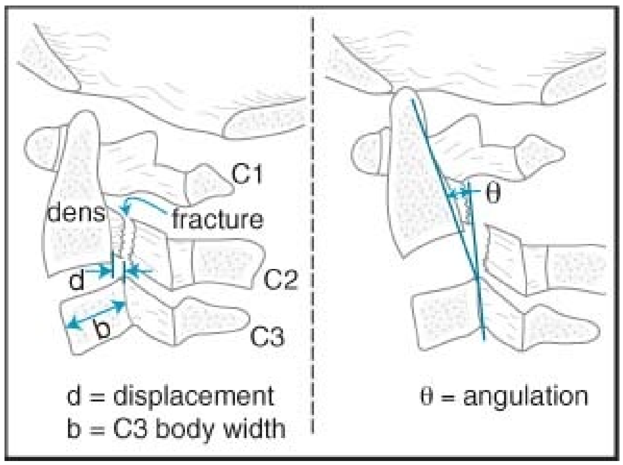


Figure 28-4 Grading system of Francis

PRESENTATION

Most (≈ 95%) are neurologically intact, those few with deficits are usually minor (paresthesias, monoparesis…) and many recover within one month[140]. Almost all conscious patients will have cervical pain usually in the upper posterior cervical region, and occipital neuralgia is not uncommon[143]. There is a high incidence of associated head injury and there will be other associated C-spine injuries (e.g. C1 fracture (*see above*) or clay shoveler's fracture (*see page 969*)) in ≈ one third, with most occurring in the upper 3 cervical levels. There are usually external signs of injury to the face and head associated with the hyperextending and axial force.

EVALUATION

Cervical CT: with sagittal & coronal reconstructions should be done to fully assess the fracture.

CTA: should be done to evaluate the vertebral arteries if fracture extends through foramen transversarium (especially Levine Type IA) and in patients with symptoms suggestive of stroke. Some recommend CTA for all C2 fractures - see

Table 28-36, page 983). Alternatively, **Angiography** or **MRA** may be done as an alternative to CTA.

★ **MRI:** cervical MRI should be done to look for C2-3 disc disruption (a marker for instability (Levine grade II) which usually requires surgical stabilization). Findings may include abnormal increased signal intensity on sagittal FLAIR or T2WI.

X-Rays: lateral C-spine x-rays show the fracture in 95% of cases. Also demonstrates C2 angulation and/or subluxation. Most fractures pass through the pars or the transverse foramen[140], 7% go through the body of C2 (also see *Miscellaneous C2 fractures*, page 967). Instability can usually be identified as marked anterior displacement of C2 on C3 (guideline[140]: unstable if displacement exceeds 50% of the AP diameter of C3 vertebral body), excessive angulation of C2 on C3, or by excessive motion on flexion-extension films.

Patients suspected of having Levine Type I fractures and are neurologically intact should have physician-supervised flexion-extension x-rays to rule out a reduced type II fracture.

TREATMENT

PRACTICE GUIDELINE 28-13 ISOLATED HANGMAN'S FRACTURE

Level III[144]

- hangman's fractures may initially be managed with external immobilization in most cases (halo or collar)
- surgical stabilization should be considered in cases of:
  - A. severe angulation of C2 on C3 (Francis II & IV, Levine II)
  - B. disruption of the C2-3 disc space (Francis V, Levine II)
  - C. or inability to establish or maintain alignment with external immobilization

Nonsurgical management produces adequate reduction in 97-100% and results in a fusion rate of 93-100%[115, 145, 146] if the external immobilization is adequately maintained for 8-14 weeks[147] (average time for healing is ≈ 11.5 weeks[140]). Specific treatment depends on the reliability of the patient and the degree of stability as described below. Most cases do well with non-halo immobilization[146].

Stable fractures (Levine Types I or IA, or Francis Grades I or II)

Treat with immobilization (Aspen or Philadelphia collar[148] (p 2326) or cervicothoracic orthosis **(CTO)** (e.g. SOMI) is usually adequate) **x** 3 months[138]. Halo-vest may be needed in unreliable patients or for combination C1-C2 fractures. Schneider reported 50 cases of Type I fracture treated with non-halo fixation, only 1 was taken to surgery and was found to already be fused.

Unstable fractures

Levine Type II

Reduce with gentle <u>cervical traction</u> (most reduce with ≤ 30 lbs[138]) with the head in slight extension (preferably in halo ring) under close x-ray monitoring to prevent "iatrogenic hanging" in cases with ligamentous instability[140]. Place in halo vest **x** 3 months. Follow patients with serial x-rays. Stabilize surgically if fracture moves.

Type II fractures with ≤ 5 mm of subluxation & angulation < 10°: once reduced, apply halo-vest and begin to mobilize (usually within 24 hrs of injury). Verify that immobilization is adequate in the halo with upright lateral C-spine x-ray, operate if inadequate. After 8-12 weeks, change to Philadelphia collar or CTO until fusion is definitely complete (usually 3-4 months).

Type II fractures with > 5 mm subluxation or ≥ 10° of angulation: Surgical fusion in these patients is recommended because of the following concerns:

1. risk of settling if immediately mobilized in halo-vest
2. healing with significant angulation may result in chronic pain
3. if not reduced, the gap may be too large for bony bridging using traction alone

Alternatively, cervical traction can be maintained for ≈ 4 weeks and then reduction should be reassessed 1 hour after removing weight from traction, and if stable, again 24 hours after mobilizing in a halo vest. If unstable, return to traction and repeat trial at 5 & 6 weeks. If still unstable at 6 weeks, surgical fusion is recommended[138].

Levine Type IIA

✖ Traction will accentuate the deformity[138]. Fractures should be reduced by immediate placement in halo vest (bypassing traction) with extension and

compression applied. Halo-vest immobilization **x** 3 months produces ≈ 95% union rate.

Levine Type III

✖ Reduction with traction may be dangerous with locked facets. ORIF is recommended[115]. MRI prior to surgery is recommended to assess the C2-3 disc. Can follow ORIF with halo-vest for the fracture, or can fuse at the same time as ORIF.

SURGICAL TREATMENT

Indications

Few patients have indications for surgical treatment of HF, and include those with:

1. inability to reduce the fracture (includes most Levine Type III & some Type II)
2. failure of external immobilization to prevent movement at fracture site
3. traumatic C2-3 disc herniation with compromise of the spinal cord[149]
4. established non-union: evidenced by movement on flexion-extension film[140], see *Flexion-extension cervical spine x-rays*, page 940 (all failures of nonoperative treatment had displacement > 4 mm[115])

Hangman's fractures likely to need surgery[141]:

1. Levine Type II or III
2. or Francis grade II, IV or V
3. or if either:
   A. anterior displacement of C2 VB > 50% of the AP diameter of the C3 VB
   B. or if angulation produces widening of either the anterior or posterior borders of the C2-3 disc space > the height of the normal C3-4 disc below

Surgical options

1. fusion techniques:
   A. posterior approach: if the fracture is not transfixed (osteosynthesis - *see below*) then a C1-2 fusion is required. This depends on the

integrity of the C2-3 disc and facet joint capsules, otherwise a C1-3 fusion is required. Occasionally the occiput is incorporated as well. Options for C1-2 fusion:

1. C1-2 wiring and fusion
2. C1-2 lateral mass screws/rods (*see page 185*)

B. anterior C2-3 discectomy[140] with fusion. Optional anterior plating via a transverse anterior cervical incision midway between the angle of the jaw and the thyroid cartilage[145, 149]

1. preserves more motion by excluding C1
2. this approach is also recommended for established non-union[140]
3. not optimal for Levine Type III requiring ORIF for locked facets
4. also used when at least a partial reduction cannot be achieved
5. technique:
   a. to maximize access at the upper end of the approach (i.e. C2):
      i. the upper and lower teeth must be approximated, which means an ET tube cannot be used. NT intubation, or if the patient has one, a tracheostomy, may be used. An OG tube also cannot be used, an NG tube is employed. Halter traction may be used for distraction and to keep the jaw closed
      ii. the head is rotated slightly away from the side of the approach to move the mandible out of the way
   b. skin incision just under the angle of the mandible (check level on fluoro or x-ray prior to making incision)
   c. intervertebral discectomy as per usual
   d. if it is intact and the MRI does not show a herniated disc, then the posterior longitudinal ligament need not be opened
   e. the end plates should be made parallel to each other
   f. anterior plating is often used to supplement
   g. halo immobilization post-op is usually employed

2. **osteosynthesis**: screw placement from posterior approach through the C2 pedicle across the fracture fragment[138 (p 443)]. Reduction must be achieved before the screw holes are drilled. The technique for C2 pedicle screws (*see page 187*) is used. The posterior fracture fragment may be overdrilled with a 3.5 mm drill. A “top hat” is placed in the hole and a 2.7 mm drill is used to drill the VB. Screw length: 30-35 mm for average adults. Alternatively, a lag screw may be used (with 20 mm unthreaded)

TREATMENT ENDPOINT

Plain x-rays should show trabeculation across the fracture site or interbody fusion of C2 to C3. Flexion-extension lateral radiographs should show no movement at the fracture site.

28.6.4.2. Odontoid fractures

Key concepts:

> - 10-15% of C-spine fx. Can occur in older patients with minor trauma (GLF), or in younger patients typically following MVA, falls froma height, skiing…
> - may be fatal at time of injury, most survivors are intact. Neck pain is common
> - classification: Anderson & D'Alonzo (*Table 28-22*). Type II is the most common
> - Tx: surgery is considered for: Type II if age > 50 yrs,, Type IIA, or Type II & III if displacement ≥ 5 mm or if alignment cannot be maintained with halo

Significant force is required to produce an odontoid fracture in a young individual, and is usually sustained in an motor vehicle accident (MVA), a fall from a height, a skiing accident, etc. In patients > 70 years age, simple ground level falls (GLF) with head trauma may produce the fracture. Odontoid fractures comprise ≈10-15% of all cervical spine fractures[150]. They are easily missed on initial evaluation, especially since significant associated injuries are frequent and may mask symptoms. Pathologic fractures can also occur, e.g. with metastatic involvement (*see page 743*).

Flexion is the most common mechanism of injury, with resultant anterior displacement of C1 on C2 (atlantoaxial subluxation). Extension only occasionally produces odontoid fractures, usually associated with posterior displacement.

Signs and symptoms

The frequency of fatalities at the time of the accident resulting directly from odontoid fractures is unknown, it has been estimated at 25-40%[151]. 82% of patients with Type II fractures were neurologically intact, 8% had minor deficits of scalp or limb sensation, and 10% had significant deficit (monoparesis to quadriplegia)[152]. Type III fractures are rarely associated with neurologic injury.

Common symptoms are high posterior cervical pain, sometimes radiating in the distribution of the greater occipital nerve (occipital neuralgia). Almost all patients with high posterior cervical pain will also have paraspinal muscle spasm, reduced range of motion of the neck, and tenderness to palpation over the upper cervical spine. A very suggestive finding is the tendency to support the head with the hands when going between the up-right and supine position. Paresthesias in the upper extremities and slight exaggeration of muscle stretch reflexes may also occur. Myelopathy may develop in patients with non-union (*see page 965*).

Classification

The classification system of Anderson and D'Alonzo[153] is shown in *Figure 28-5* and *Table 28-22*.

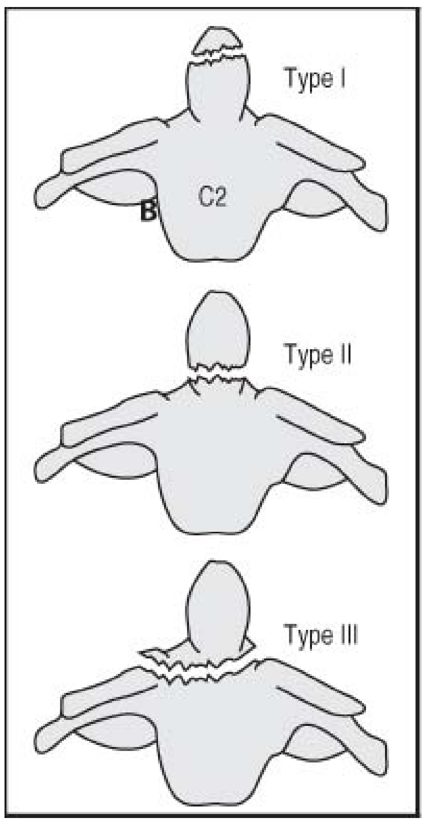


Figure 28-5 Major types of odontoid fractures (AP view)

Table 28-22 Classification of odontoid fractures

Type	Characteristics	Stability
I	through tip (above transverse ligament), rare	unstable*

II	through base of neck, the most common dens fracture (may be best seen on AP x-ray)	usually <u>unstable</u>
IIA	similar to type II, but with large bone chips at fracture site[154], comprise ≈ 3% of type II odontoid fractures. Diagnosed by plain radiographs and/or CT	usually <u>unstable</u>
III	through body of C2 (usually involves marrow space). May involve superior articular surface	usually stable

* controversial, see text

Type I fractures are due to avulsion of the attachment of the alar ligament. They are very rare. Although long considered to be a stable injury, they may not occur as an isolated fracture and may be a manifestation of atlanto-occipital dislocation[155]. Also, it may be a marker for possible disruption of the transverse ligament[156] which may result in atlanto-axial instability.

Imaging pearl: a type III odontoid fracture may be misinterpreted as type II on sagittal CT reconstructions because the fracture appears to lie above the VB. Always check the coronal reconstruction which more readily demonstrates the relationship of the fracture to the VB.

TREATMENT

PRACTICE GUIDELINE 28-14 ISOLATED ODONTOID FRACTURES

Level II[144]: <u>isolated</u> Type II odontoid fractures in adults ≥ 50 years age should be considered for surgical stabilization & fusion

Level III[144]

- Type I, II & III fractures may be managed initially with external cervical immobilization
- Type II & III: consider surgical fixation for:
  - A. fracture displacement ≥ 5 mm
  - B. or Type IIA fracture (comminution)
  - C. or inability to maintain alignment with external immobilization

TYPE I

So rare that meaningful analysis is difficult. Due to possible associated atlanto-axial instability, surgical fusion may at times be necessary.

Type II

Treatment remains controversial. No agreement has been reached after many attempts to identify factors that will predict which type II fractures are most likely to heal with immobilization and which will require operative fusion. Critical review of the literature reveals a paucity of well designed studies. A wide range of nonunion rates with immobilization alone (5-76%) is quoted: **30%** is probably a reasonable estimate for overall nonunion rate, with 10% nonunion rate for those with displacement < 6 mm[157]. Possible key factors in predicting nonunion include:

1. degree of displacement: probably the most important factor
   A. some authors feel that displacement > 4 mm increases nonunion[153, 158]
   B. some authors use ≥ 6 mm as the critical value, citing a 70% nonunion rate[147] in these regardless of age or direction of displacement
2. age:
   A. children < 7 yrs old almost always heal with immobilization alone
   B. some feel that there is a critical age above which the nonunion rate increases, and the following ages have been cited: age > 40 yrs (possibly ≈ doubling the nonunion rate)[158], age > 55 yrs[159], age > 65 yrs[160], yet others do not support increasing age as a factor[157]

Indications for surgery

Given the above, there can be no hard and fast rules. The following is offered as a guideline (also, see *isolated odontoid fractures* above).

★ Surgical treatment (instead of external immobilization) is recommended for odontoid Type II fractures in patients ≥ 7 years age with any of the following:

1. displacement ≥ 5 mm
2. instability at the fracture site in the halo vest (*see below*)
3. age ≥ 50 years: increases nonunion rate (with halo) 21-fold[161]
4. nonunion (*see Table 28-24* for radiographic criteria) including firm fibrous union[162], especially if accompanied by myelopathy[143]
5. disruption of the transverse ligament: associated with delayed instability[123]

Surgical options

1. odontoid compression screw: appropriate for acute type II fractures with

transverse ligament intact and attached (*see page 181*)

2. C1-2 arthrodesis: *see page 184* for options including wiring/fusion, transarticular screws, halifax clamps…

Immobilization

For those not meeting surgical indications above, 10-12 weeks of immobilization as suggested in *Table 28-23* is recommended. There is no Class I medical evidence comparing immobilization options.

Halo vest: fusion rate = 72%[157], appears superior to a SOMI. If a halo is used, obtain supine and upright lateral C-spine x-rays in the halo. If there is movement at the fracture site, then surgical stabilization is recommended.

Rigid collar[157, 163]: fusion rate = 53%.

In patients who are poor surgical candidates, there is theoretical and anecdotal rationale to consider calcitonin therapy (*see page 993*) in conjunction with a rigid cervical orthosis[164].

Table 28-23 Immobilization for odontoid fractures

Fracture Type	Option
Type I	collar, halo
Type II*	halo, collar*
Type IIA*	halo*
Type III*	collar, halo*

* consider surgery for these, use indicated brace when surgery not deemed appropriate

Table 28-24 Radiographic criteria of nonunion of odontoid fractures

1. defect in the dens with contiguous sclerosis of both fragments (vascular pseudarthrosis)
2. defect in the dens with contiguous resorption of both fragments (rarefying osteitis or atrophic pseudarthrosis)
3. defect in the dens with definite loss of cortical continuity
4. movement of dens fragment demonstrated on flexion-extension x-rays

Nonunion

The most common symptom of nonunion is continued high posterior cervical pain beyond the time that the brace is removed. Late myelopathy can develop in as many as 77% of mobile nonunions[151, 165] as a result of motion and soft tissue proliferation around the unstable fracture site. The radiographic criteria for

nonunion are shown in *Table 28-24*.

Type IIA

Early surgery is recommended for all type IIA fractures[154].

Type III

≈ 90% heal with external immobilization (and analgesics) if adequately maintained for 8-14 weeks[147]. Halo-vest brace is probably best[163], fusion rate ≈ 100% in 1 series[157]. Rigid collar: fusion rate = 50-70%; if used, monitor the patient with frequent C-spine x-rays to rule-out nonunion.

Surgical treatment

See *Atlantoaxial fusion (C1-2 arthrodesis)* on page 183 and *Anterior odontoid screw fixation* on page 181 for surgical options and operative details.

OS ODONTOIDEUM

PRACTICE GUIDELINE 28-15 OS ODONTOIDEUM

Diagnosis

Level III[171]

- recommended: the following plain C-spine x-rays: AP, open-mouth odontoid, lateral (static & flexion-extension)
- consider: tomography (CT or plain) and/or MRI of craniocervical junction

Management

Level III[171]

- patients without neurologic signs or symptoms (even with C1-2 instability) may be followed with clinical & radiographic surveillance
- those with neurologic signs or symptoms and C1-2 instability
    A. may be managed with posterior C1-2 internal fixation and fusion
    B. options:
        1. posterior wiring & fusion. Post-op halo immobilization is recommended following these procedures
        2. C1-2 transarticular screw fixation and fusion: successful screw placement seems to obviate the need for post-op halo

- consider occipitocervical fusion with or without C1 laminectomy for patients with irreducible cervicomedullary compression and/or evidence of associated occipitoatlantal instability
- consider transoral decompression in patients with irreducible ventral cervicomedullary compression

A separate bone ossicle of variable size with smooth cortical borders separated from a foreshortened odontoid peg, occasionally may fuse with the clivus. May mimic Type 1 or 2 odontoid fracture. Etiology is debated with evidence to support both of the following (diagnosis & treatment do not depend on which etiologic theory is correct):

1. congenital: developmental anomaly (nonunion of dens to body of axis). However, does not follow known ossification centers (*see page 137*), and has been demonstrated in 9 patients with previously normal odontoid processes[166]
2. acquired: postulated to represent an old nonunion fracture or injury to vascular supply of developing odontoid[166, 167]

True os odontoideum is rare. **Ossiculum terminale**: nonunion of the apex at the *secondary* ossification center, is more common.

Two anatomic types:

1. **orthotopic**: ossicle moves with the anterior arch of C1
2. **dystopic**: ossicle is functionally fused to the basion. May sublux anterior to the C1 arch

Presentation

Main groups identified in the literature[168]:

1. occipitocervical/neck pain
2. myelopathy: further subdivided[166]
   A. transient myelopathy: common following trauma
   B. static myelopathy
   C. progressive myelopathy
3. intracranial signs or symptoms: from vertebrobasilar ischemia
4. incidental finding

Most patients are neurologically intact and present with atlantoaxial instability which may be discovered incidentally. Many symptomatic and

asymptomatic patients have been reported with no new problems over many years of follow-up[169]. Conversely, cases of precipitous spinal cord injury after seemingly minor trauma have been reported[170].

> Σ The natural history is variable, and predictive factors for deterioration, especially in asymptomatic patients, have not been identified[171].

Evaluation

For diagnosis, see *os odontoideum* below.

It is critical to R/O C1-2 instability. However, myelopathy does not correlate with the degree of C1-2 instability. An AP canal diameter < 13 mm does correlate with the presence of myelopathy.

Treatment

Regardless of whether os odontoideum is congenital or an old non-union fracture, immobilization is unlikely to result in fusion. Therefore, when treatment is elected, surgery is required (usually atlantoaxial arthrodesis, *see page 183*).

28.6.4.3. Miscellaneous C2 fractures

Comprise ≈ 20% of C2 fractures[115]. Includes fractures of spinous process, lamina, facets, lateral mass or C2 vertebral body. Fractures of spinous process or lamina may be treated with Philadelphia collar or cervicothoracic orthosis **(CTO)**. Fractures which compromise the anterior or middle columns (i.e. fractures of facets, C2 body, or lateral mass) requires CTO or halo-vest if nondisplaced, or halo if displaced.

PRACTICE GUIDELINE 28-16 FRACTURES OF THE AXIS (C2) BODY

Treatment

Level III[144]: external immobilization is recommended for isolated axis body fractures

28.6.5. Combination C1-2 injuries

Combination C1-2 injuries are relatively common and may imply more significant structural and mechanical injury than isolated C1 or C2 fractures. The frequency of C2 fractures in C1-2 combination injuries is shown in *Table 28-25*. 5-53% of patients with Type II or III odontoid fractures and 6-26% of hangman's fractures have an associated C1 fracture[172].

Table 28-25 Accompanying C2 injuries

Injury	%
Type II dens fracture	40%
Type III dens fracture	20%
hangman's fracture	12%
other	28%

Treatment

PRACTICE GUIDELINE 28-17 COMBINATION ATLAS & AXIS FRACTURES

Level III[172]

- recommended: base treatment primarily on the type of C2 injury
- recommended: external immobilization of most C1-2 fractures
- consider surgical stabilization* for these situations†:
  - A. C1-Type II odontoid combination fractures with an ADI ≥ 5 mm
  - B. C1-hangman's combination fractures with C2-3 angulation ≥ 11°

* loss of integrity of the C1 ring may necessitate modification of the surgical technique

† these injuries are potentially unstable (see Axis (C2) fractures on page 959)

Treatment options[172] are summarized in *Table 28-26*.

Table 28-26 Treatment options for combination C1-C2 injuries

Injury	Treatment options
C1 + hangman's	
stable	collar, halo, surgery*

untable (C2-3 angulation ≥ 11°)	halo, surgery
C1 + Type II odontoid fracture	
stable (ADI* < 5 mm)	collar, halo, surgery
unstable (ADI ≥ 5 mm)	halo, surgery
C1 + Type III odontoid fracture	halo
C1 + miscellaneous C2	collar, halo

* abbreviations: ADI = atlantodental interval; surgery = surgical fixation & fusion

Outcome

Only 1 nonunion (C1-Type II odontoid, treated initially with halo). No new neuro deficits.

28.6.6. Subaxial (C3 through C7) injuries/fractures

Classification systems

Various systems have been proposed to help assess stability and/or guide management. A descriptive system by Allen, et al (*see below*) is based on the mechanism of injury. Attempts at quantifying biomechanical stability include the White and Panjabi system (*see page 969*) and the recently proposed subaxial injury classification **(SLIC)** (*see below*). Measurements for spine injuries are based on methods outlined by Bono et al.[173].

Cervical spine injury classification on the basis of mechanism of trauma

A system adapted from Allen et al.[176] divides cervical spine fracture/dislocations into 8 major groups based on the dominant loading force and neck position at the time of injury as shown in *Table 28-27*. Grades of severity within each group are described, and any of these fractures may also be associated with damage from rotatory loads.

Details on some of these fracture types are provided in following sections.

Table 28-27 Examples of types of cervical spine injuries*

Major loading force	Acting alone	With compression	With distraction
Flexion (970)	unilateral or bilateral facet dislocation (972)	• anterior VB fx. with kyphosis • disruption of interspinous ligament • teardrop fx. (970)	• torn posterior ligaments (may be occult) • dislocated or locked facets (972)
Extension† (974)	fractured spinous process and possibly lamina†	fracture through lateral mass or facet† (including horizontalization of facet) (976)	disruption of ALL with retrolisthesis of superior vertebrae on inferior one†
Neutral position		burst fracture (970)	complete ligamentous disruption (very unstable)

* abbreviations: ALL = anterior longitudinal ligament; VB = vertebral body, fx = fracture; numbers in parentheses are page numbers for that topic

† any of the extension injuries may produce SCIWORA in young patients, or central cord syndrome in the presence of stenosis

Spine Trauma Study Group subaxial cervical spine injury classification

The subaxial injury classification **(SLIC)**[174] (*Table 28-29*) includes injuries to the disco-ligamentous complex **(DLC)** in addition to neurologic and bony injuries. This system demonstrates moderate reliability.

DLC integrity[174]: The DLC includes: anterior longitudinal ligament (the strongest component of the anterior DLC), posterior longitudinal ligament, ligamentum flavum, facet capsule (the strongest component of the posterior DLC), interspinous and supraspinous ligaments. The DLC is the hardest SLIC parameter to evaluate. Largely inferred indirectly from MRI findings. Healing is less predictable than bone healing in the adult. More data needs to be accrued before this parameter can be reliably quantified.

Management guidelines

Table 28-28 Management based on total SLIC score

SLIC score	Management
1-3	non surgical
4	not specified
≥ 5	surgical

Table 28-29 Subaxial injury classification (SLIC)[174]

Injury (rate <u>the most severe injury</u> at that level)	Points
Morphology	
No abnormality	0
Simple compression (compression fx, endplate disruption, sagittal or coronal plane VB fx.)	1
Burst fracture	2
Distraction (perched facet, posterior element fx.)	3
Rotation/translation (facet dislocation, teardrop fx., advanced compression injury, bilateral pedicle fx., floating lateral mass (*page 976*)…). Guidelines: relative axial rotation ≥ 11°[175] or any translation not related to degenerative causes	4
Discoligamentous complex (DLC)	
Intact	0
Indeterminate (isolated interspinous widening with < 11° relative angulation & no abnormal facet alignment, ↑ signal on T2WI MRI in ligaments…)	1
Disrupted (perched or dislocated facet, < 50% articular apposition, facet diastasis > 2 mm, widened anterior disc space, ↑ signal on T2WI MRI through entire disc…)	2
Neurologic status	
Intact	0
Root injury	1
Complete spinal cord injury	2
Incomplete spinal cord injury	3
• Continuous cord compression with neuro deficit	+1

Description using the SLIC

A given injury can be described as follows:

1. spinal level
2. <u>SLIC morphology</u> (from *Table 28-29*): use the most severe injury type at this level
3. description of bony injury: e.g. fracture or dislocation of transverse process, pedicle, endplate, superior or inferior articular process, lateral mass…
4. <u>SLIC DLC status</u> (from *Table 28-29*) with descriptors: e.g. herniated disc…
5. <u>SLIC neurologic status</u> (from *Table 28-29*)
6. confounders: e.g. presence of ankylosing spondylitis, DISH, osteoporosis, previous surgery, degenerative disease…

STABILITY MODEL OF WHITE & PANJABI

Guidelines for determination of *clinical* instability (*see page 930*) of the subaxial cervical spine published by White and Panjabi[1 (p 314)] are shown in *Table 28-30*. In general, compromise of anterior elements produces more instability in extension, whereas compromise of the posterior elements produces more instability in flexion (important in patient transfers and immobilization). NB: certain conditions such as ankylosing spondylitis may cause an otherwise stable injury to be unstable (*see page 502*).

Stretch test: The cervical stretch test may be helpful in cases where stability is difficult to determine based on other factors. It may also be useful in detecting instability in cases such as an athlete with no obvious bony or ligamentous disruption. It is performed by applying graduated cervical traction with the patient lying supine on an x-ray table. Serial neurologic exams and lateral radiographs are performed as outlined in the footnote of *Table 28-30*.

CLAY SHOVELER'S FRACTURE

Avulsion of spinous processes (usually C7) first described in Perth, Australia (path-omechanics: during the throwing phase of shovelling, clay may stick to the shovel jerking the trapezius and other muscles which are attached to cervical spinous processes)[178]. Can also occur with: whiplash injury[179], injuries that jerk the arms upwards (e.g. catching oneself in falling), neck hyperflexion, or a direct blow to the spinous process.

This fracture is stable, and by itself poses little risk. If the patient is intact, they should have further study (flexion-extension C-spine x-rays or CT scan through the affected level) to R/O other occult fractures. A rigid collar is used PRN pain.

VERTICAL COMPRESSION INJURIES

In order to apply a purely compressive force to the cervical spine, reversal of the normal cervical lordosis is required, as may occur in a slightly flexed posture. Burst fractures are the most common result, with the possibility of retropulsion of bone into the spinal canal.

FLEXION INJURIES OF THE SUB-AXIAL CERVICAL SPINE

Constitutes up to 15% of cervical spine trauma. Common causes include:

MVAs, falls from a height, and diving into shallow water[180].

Table 28-30 Guidelines for diagnosing clinical instability of the mid & lower C-spine[1]

Item	Points*
anterior elements† destroyed or unable to function	2
posterior elements† destroyed or unable to function	2
positive **stretch test**‡	2
spinal cord damage	2
nerve root damage	1
abnormal disc narrowing	1
developmentally narrow spinal canal, either • sagittal diameter < 13 mm, OR • Pavlov ratio§ < 0.8	1
dangerous loading anticipatedΔ	1
Radiographic criteria	
• neutral position x-rays sagittal plane displacement > 3.5 mm or 20% relative sagittal plane angulation > 11°	2 2
OR	
• flexion-extension x-rays sagittal plane translation > 3.5 mm or 20% sagittal plane rotation > 20°	2 2
Unstable if total ≥ 5	

* if there is inadequate information for any item, add half of the value for that item to the total

† in the C-spine, posterior elements = anatomic components posterior to the posterior longitudinal ligament

‡ stretch test: apply incremental cervical traction loads of 10 lbs q 5 mins up to 33% body wt. (65 lbs max). Check Xray and neuro exam after each Δ. Positive if Δ in separation > 1.7 mm or Δ angle > 7.5° on x-ray or change in neuro exam. This test is contraindicated if obvious instability

§ **Pavlov ratio** = the ratio of (distance from the midlevel of the posterior VB to the closest point on the spinolaminar line): (the AP diameter of the middle of the VB)

Δ e.g. heavy laborers, contact sports athletes, motorcyclists

Compression flexion injuries

The classic diving injury is the prototypical example. Posterior element fractures occur in up to 50% of compression flexion injuries[181]. Although flexion-compression injuries do distract the posterior elements to some degree, most do not produce posterior ligamentous injuries. Sub-types include: teardrop fractures (*see below*), quadrangular fractures (*see page 971*).

Treatment: mild cervical compression fractures without neurologic deficit or retropulsion of bone into the spinal canal are usually treated with a rigid orthosis until x-rays show healing has occurred (usually 6-12 wks). Stability is assessed with flexion-extension views (*see page 940*) before discontinuing the brace. More severe compression fractures heal in a halo brace with ≈ 90% rate of ankylosing fusion.

Teardrop fractures

Originally described by Schneider & Kahn[182]. Results from hyperflexion or axial loading at the vertex of the skull with the neck flexed (eliminating the normal cervical lordosis)[183] (often mistakenly attributed to hyperextension because of the retrolisthesis). There are varying degrees of severity. In its most severe form, the injury consists of complete disruption of all of the ligaments, the facet joints and the intervertebral disk[184]. An important feature is displacement of the inferior margin of the fractured vertebral body posteriorly into the spinal canal[182]. Usually unstable.

Seen in ≈ 5% of patients in a large series with x-ray evidence of cervical spine trauma[90]. Patients are often quadriplegic, although some may be intact and some may have anterior cervical cord syndrome (*see page 950*). Possible associated injuries and radiographic findings include[184, 185]:

1. a small chip of bone (the "teardrop") just beyond the anterior inferior edge of the involved vertebral body **(VB)** on lateral cervical spine film
2. often associated with a fracture through the sagittal plane of the VB (**sagittal split**) which can usually be seen on AP view. Thin cut CT scan is more sensitive
3. a large triangular fragment of the anterior inferior VB
4. other fractures through the vertebral body may also occur
5. the fractured vertebrae is usually displaced posteriorly on the vertebra below (easily appreciated on oblique x-rays, see *Figure 28-6*, page 972). However, cases without retrolisthesis are also described[181]
6. the fractured body is often wedged anteriorly (kyphosis), and may also be wedged laterally
7. disruption of the facet joints which may be appreciated as separation of the joints on lateral x-ray, often unmasked by cervical traction
8. prevertebral soft-tissue swelling (*see page 136*, for measurements)
9. narrowing of the intervertebral disc below the fracture (indicating disruption)

Distinguishing between teardrop fracture and avulsion fracture

Rationale: Teardrop fractures must be distinguished from a simple **avulsion fracture** which may also result in a small chip of bone off the anterior inferior VB, usually pulled off by traction of the anterior longitudinal ligament **(ALL)** in hyperextension. Although there may be disruption of the ALL in these cases, it does not usually cause instability.

Methodology: In a patient with a small bone chip off of the inferior anterior VB, a "tear-drop" fracture needs to be ruled-out. Determine if the following criteria are met:

- neurologically intact (because of the need for cooperation, this includes mental status, and excludes the inebriated or concussed patient)
- size of bone fragment is small
- no malalignment of vertebral bodies
- no evidence of VB fracture in sagittal plane on AP C-spine x-rays or on CT
- no posterior element fracture on x-ray or CT
- no prevertebral soft tissue swelling at level of fragment (*see page 136*)
- and no loss of vertebral body height or disc space height

If the above criteria are met, obtain flexion-extension C-spine x-rays (see *Flexion-extension cervical spine x-rays*, page 940). If no abnormal movement, discharge patient in rigid collar (e.g. Philadelphia collar), and repeat the films in 4-7 days (i.e. after the pain has subsided to be certain that alignment is not being maintained by cervical muscle spasm from pain), D/C collar if 2nd set of films is normal.

If the patient does not meet the above criteria, treat them as an unstable fracture and obtain a CT scan through the fractured vertebra to evaluate for associated fractures (e.g. sagittal plane fracture that may not be apparent on plain x-ray).

MRI assesses the integrity of the disc and gives some information about the posterior ligaments.

Treatment of teardrop fracture

If the disc and ligaments are intact (determined by MRI) then an option is to employ a halo brace until the fragment is healed (perform flexion-extension x-

rays after removing the halo to rule-out persistent instability). Alternatively, surgical stabilization may be performed, especially if ligamentous or disc injury is seen on MRI. When the injury is primarily posterior due to disruption of the posterior ligaments and facet joints, and if there is no anterior compromise of the spinal canal, then posterior fusion suffices (e.g. *see page 179*). Severe injuries with canal compromise often require a combined anterior decompression and fusion (performed first) followed by posterior fusion using either a modified Bohlman triple-wire technique or lateral mass screws and rods.

Quadrangular fractures[186]

Four features:

1. oblique vertebral body **(VB)** fracture passing from anterior-superior cortical margin to inferior end plate
2. posterior subluxation of superior VB on the inferior VB
3. angular kyphosis
4. disruption of disc and anterior and posterior ligaments

Treatment: May require combined anterior and posterior fusion.

Distraction flexion injuries

Ranges from hyperflexion sprain (mild, *see below*) to minor subluxation (moderate) to bilateral locked facets (severe, *see below*). Posterior ligaments are injured early and are usually evidenced by widening of the interspinous distance (*see page 137*).

Hyperflexion sprain

A purely ligamentous injury that involves disruption of the posterior ligamentous complex without bony fracture. May be missed on plain lateral C-spine x-rays if they are obtained in normal alignment (requires flexion-extension views, see *Flexion-extension cervical spine x-rays*, page 940). Instability may be concealed when films are obtained shortly after the injury if spasm of the cervical paraspinal muscles splints the neck and prevents true flexion[187]. For patients with limited flexion, a rigid collar should be prescribed, and if the pain persists 1-2 weeks later the films should be repeated (including flexion-extension).

Radiographic signs of hyperflexion sprain[188] (x-rays may also be normal):

1. kyphotic angulation

2. anterior rotation and/or slight (1-3 mm) subluxation
3. anterior narrowing and posterior widening of the disc space
4. increased distance between the posterior cortex of the subluxed vertebral body and the anterior cortex of the articular masses of the subjacent vertebra
5. anterior and superior displacement of the superior facets (causing widening of the facet joint)
6. fanning (abnormal widening) of the interspinous space on lateral C-spine x-ray, or increased interspinous distance on AP (see *Interspinous distances*, page 137)

Subluxation

Cadaver studies have shown that horizontal subluxation **> 3.5 mm** of one vertebral body on another, or > 11° of angulation of one vertebral body relative to the next indicates ligamentous instability[189, 190] (see *Table 28-30*, page 970). Thus, if subluxation of ≤ 3.5 mm on plain films is seen, and there is no neuro deficit, obtain flexion-extension films (see *Flexion-extension cervical spine x-rays*, page 940). If no abnormal movement, remove cervical collar.

Locked facets

Severe flexion injuries can result in **locked facets** (AKA "sprung" facets AKA "jumped" facets) with reversal of the normal "shingled" relationship between facets (normally the inferior facet of the level above is posterior to the superior facet of the level below). Involves disruption of facet capsule. Facets that have not completely locked but have had significant ligamentous disruption allowing distraction just short of the point of locking are known as "**perched facets**".

Flexion + rotation → unilateral locked facets. Hyperflexion → bilateral locked facets.

Unilateral locked facets:

25% of patients are neurologically intact, 37% have root deficit, 22% have incomplete cord injuries, and 15% are complete quadriplegics[191].

Bilateral locked facets:

Occurs with disruption of ligaments of apophyseal joints, ligamentum flavum, longitudinal and interspinous ligaments, and the anulus. Rare. Most common at C5-6 or C6-7. 65-87% have complete quadriplegia, 13-25% incomplete, ≤ 10% are intact. Adjacent fractures (VB, facet, lamina, pedicle…)

occur in 40-60%[176, 192]. Nerve root deficits may also occur.

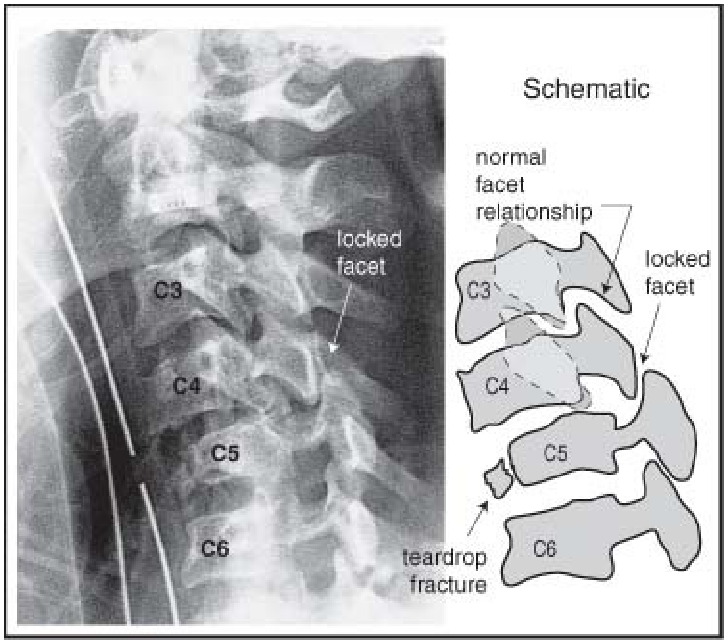


Figure 28-6 Unilateral locked facets (left C4 on C5) & C5 **tear-drop fracture** (see page 970) 60° LAO C-spine x-ray on left, and schematic on right (sagittally oriented VB fracture through C5 seen on CT scan, not shown). Note the anterior subluxation of C4 on C5, and the slight retrolisthesis of C5 on C6

Diagnosis

C-spine x-rays: both unilateral **(ULF)** and bilateral locked facets **(BLF)** will produce subluxation (ULF → rotatory subluxation).

BLF (bilateral locked facets): usually produces > 50% subluxation on lateral C-spine xray.

ULF (unilateral locked facets):

1. AP: spinous processes above the subluxation rotate to the same side as the locked facet (with respect to those below)
2. lateral: "**bow-tie sign**" (visualization of left & right facets at the level of the injury instead of the normal superimposed position[191]). Subluxation may be seen. Disruption of the posterior ligamentous complex may produce widening of the interspace between spinous processes
3. oblique (*see Figure 28-6*): may demonstrate the locked facet which will be seen blocking the neural foramen (use ≈ 60° LAO for left locked facet, 60° RAO for right)

CT: "**naked facet sign**": the articular surface of the facet will be seen with

the appropriate articulating mate either absent or on the wrong side of the facet (*see Figure 28-7*). With ULF, CT also demonstrates the rotation of the level above anteriorly on the level below on the side of the locked facet.

MRI: the best test to rule-out traumatic disc herniation (found in 80% of BLF)[193].

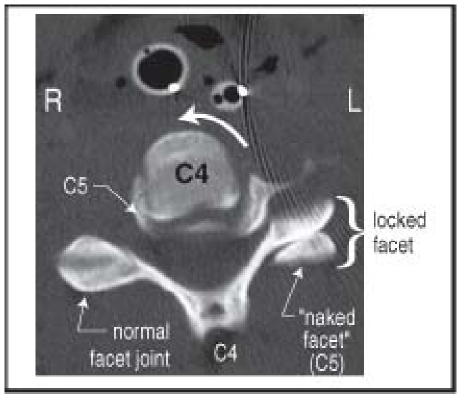


Figure 28-7 Locked facet (left C4-5). (CT scan). Note the rotation of the C4 vertebral body on C5 (curved arrow)

Treatment

PRACTICE GUIDELINE 28-18 SUBAXIAL FACET DISLOCATIONS*

Level III[177]

- initial treatment: closed or open reduction is recommended
- subsequent treatment
  - A. rigid external immobilization, anterior arthrodesis with plate fixation, or posterior arthrodesis with plate or rod or interlaminar clamp fixation
  - B. prolonged bedrest in traction if the above treatment options are not available

* excluding facet dislocations, see page 973 for those injuries

Closed reduction of locked facets: ✖ Contraindicated if traumatic disc herniation is demonstrated on MRI. Patients who cannot be assessed neurologically may be done using SSEP monitoring. Two methods of closed reduction:

1. **traction**: more commonly employed in the U.S.

A. initial weight (in lbs) ≈ **3 x cervical vertebral level**, increase in 5-10 lb increments usually at 10-15 minute intervals until desired alignment is attained (assess neurologic exam (or SSEP/MEP) and lateral C-spine x-ray or fluoroscopy after each Δ to avoid overdistraction)

B. end points (i.e. stop the procedure):
  - usually **do not exceed 10 lbs per vertebral level** (some say 5 lbs/level). This is just a guideline to avoid overdistraction
  - distraction of perched/locked facet or desired reduction is achieved
  - if occipitocervical instability develops
  - if any disc space height exceeds 10 mm (overdistraction)
  - if any neurologic deterioration or deterioration of SSEP/MEP

C. with unilateral locked facets, one may add gentle manual torsion towards the side of the locked facets. With bilateral locked facets, one may add gentle manual posterior tension (e.g. with a rolled towel under the occiput)

D. once the facets are perched or distracted, gradual reduction of the weights will usually result in reduction - verify with x-ray (placing the neck in slight extension, e.g. with small shoulder roll, may help maintain the reduction)

2. **manipulation**: less commonly accepted[191]. Involves manually applying axial traction and sagittal angulation sometimes with rotation and direct pressure at the fracture level under fluoroscopy

Paraspinal muscle relaxation (but not enough to cause obtundation) may assist in reduction. Use IV diazepam (Valium®) and/or narcotic. General anesthesia may be used in difficult cases (with SSEP/MEP monitoring).

Once reduction is achieved, the patient is left in 5-10 lbs of traction for stabilization.

Disadvantage of closed reduction

1. fails to reduce ≈ 25% of cases of BLF
2. risks overdistraction at higher levels or worsening of other fractures
3. neurologic worsening following closed reduction may occur with traumatic disc herniation[192, 194] and should be evaluated immediately with MRI and if confirmed treated with prompt discectomy
4. adds time and potentially pain to the patient’s care, especially since many will go on to have surgical fusion anyway

Following closed reduction, the need for internal (operative) stabilization vs. external stabilization (i.e. bracing) may be addressed (see *Stabilization* below).

Open reduction and fixation is usually required if reduction is not achieved. Closed reduction is often more difficult with bilateral locked facets than with unilateral.

Open reduction of locked facets:

1. posterior approach: the most common approach. Although rare, still subjects the patient to risk of deterioration from traumatically herniated disc. Therefore a pre-op MRI should be done if possible. Often requires drilling of the superior aspect of the articular facet of the level below. A foraminotomy is recommended when there are root symptoms to visualize and decompress the root
2. anterior approach: by removing the disc at the subluxed level and exploring the anterior epidural space, the risk of worsening deficit due to a traumatic herniated disc is theoretically reduced. Reduction may be achieved by adding simultaneous manual traction
3. combined anterior/posterior (360°) approach: using anterior plate and posterior lateral mass screws/rods eliminates need for post-op external immobilization

Stabilization: Surgical fusion is commonly performed after successful closed reduction, failed closed reduction, or following open reduction.

If there are fracture fragments about the articular surfaces, there may be satisfactory healing with halo vest immobilization (for 3 months) once closed reduction is achieved[195]. Frequent x-rays are needed to rule-out redislocation[196]. Flexion-extension x-rays are obtained upon halo removal and surgery is required for continued instability. Up to 77% of patients with unilateral or bilateral facet dislocation (with or without facet fracture fragments) will have a poor anatomic result with halo vest alone (although late instability was uncommon), suggesting that surgery should be considered for all of these patients[197]. Surgical fusion is more clearly indicated in cases without facet fracture fragments (ligamentous instability alone may not heal) or if open reduction is required.

If surgery is indicated, an MRI should be done beforehand if possible. A posterior approach is preferred if there are no anterior masses (such as traumatic disc herniation or large osteophytic spurs), if subluxation of the bodies is > one third the VB width (suggesting severe posterior ligamentous injury), or for fractures of the posterior elements. A posterior approach is mandatory if there is an unreducible dislocation. Options for posterior approach: see *Choice of posterior technique*, page 978.

EXTENSION INJURIES OF THE SUBAXIAL CERVICAL SPINE

EXTENSION INJURY WITHOUT BONY INJURY

Extension injuries can produce spinal cord injury **(SCI)** without evidence of bony injury. Injury patterns include central cord syndrome (*see page 948*) usually in an older adult with cervical spondylosis, and SCIWORA (*see below*) usually in young children. Middle aged adults with hyperextension dislocations that reduce spontaneously immediately may present with SCI and no bony abnormality on x-ray, but there may be rupture of the anterior longitudinal ligament and/or intervertebral disc on MRI or autopsy. Extension forces may also be associated with carotid artery dissections (*see page 1163*).

SPINAL CORD INJURY WITHOUT RADIOGRAPHIC ABNORMALITY ***(SCIWORA)***

Although spinal cord injuries are uncommon in children, there is a subgroup of these in which no radiographic evidence of bony or ligamentous disruption can be demonstrated (including on dynamic flexion-extension x-rays). This is attributed to the normally increased elasticity of the spinous ligaments and paravertebral soft-tissue in the young population[199] and has been dubbed SCIWORA (an acronym for "Spinal Cord Injury Without Radiographic Abnormality"). The age range of children with SCIWORA is 1.5-16 yrs, it has a much higher incidence in age ≤ 9 yrs[11]. The spinal cord may undergo contusion, transection, infarction, stretch injuries, or meningeal rupture. Additional etiologies include: blunt abdominal trauma with disruption of blood flow from the aorta or segmental branches, traumatic disc herniation. There may be an increased risk of SCIWORA among young children with asymptomatic Chiari I malformation[200].

54% of children had a delay between injury (at which time some children experience transient numbness, paresthesias, Lhermitte's sign, or a feeling of total body weakness) and the onset of <u>objective</u> sensorimotor dysfunction ("latent period") ranging from 30 minutes to 4 days.

PRACTICE GUIDELINE 28-19 SCIWORA

Diagnosis

Level III[198]

- recommended: plain C-spine x-rays and spinal CT through the suspected level of injury to R/O occult fractures

- MRI of the region of suspected injury may provide useful diagnostic information
- consider: plain x-rays of the entire spinal column

✖ not recommended: spinal angiography or myelography

Treatment

Level III[198]

- recommended: external immobilization until stability is confirmed with flexion-extension x-rays
- consider: external immobilization of the injured spinal segment for up to 12 weeks
- consider: avoidance of "high-risk" activities for up to 6 months after SCIWORA

Prognosis

Level III[198]

- MRI through the region of neurologic injury may provide useful information about neurologic outcome after SCIWORA

Radiographic evaluation

In addition to plain films and flexion-extension films (to identify overt instability which would require surgical fusion), should include MRI which may show increased signal within the spinal cord parenchyma on T2WI. There were no intraspinal space occupying lesions in 13 patients studied with myelography/CT[199].

Management

Surgical intervention, including laminectomy, has shown no benefit in the few cases where it has been tried[202].

Due to a 20% rate of repeat injury (some due to trivial trauma, and some without identifiable trauma) within 10 weeks of the original trauma when treated with only a rigid collar and restriction of contacts sports (both for 2 months), more aggressive measures were initially recommended (*see Table 28-31*).

Table 28-31 Treatment protocol for SCIWORA (modified[201])

- admit patient to hospital (helps emphasize seriousness of injury)
- BR with rigid cervical collar until flexion-extension films are normal
- MRI of cervical spine to document presence of spinal cord injury
- detailed discussion with patient and family about seriousness of injury and rationale for treatment outlined here
- immobilization in Guilford brace for 3 months*
- prohibition of contact and noncontact sports
- regular follow-up visits for monitoring condition and compliance
- liberalize activities at 3 months if flexion-extension films are normal

* this represents a conservative recommendation, a less restrictive recommendation is immobilization for 1-3 weeks[202] (see *PRACTICE GUIDELINE 28-19 SCIWORA*)

MINOR EXTENSION INJURIES

Includes spinous process and lamina fractures. By themselves, are stable.

EXTENSION COMPRESSION INJURY

This is the most common mechanism of lateral mass/facet fractures (*see below*).

LATERAL MASS AND FACET FRACTURES OF THE CERVICAL SPINE

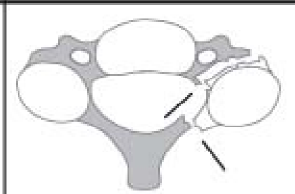
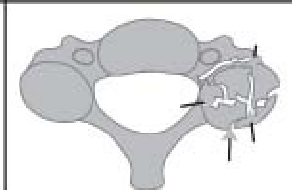
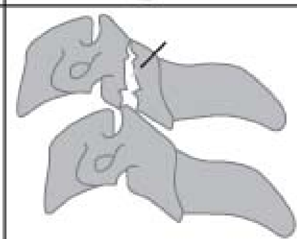
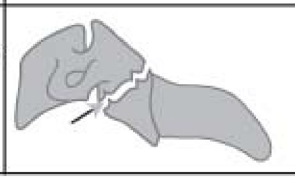
Classification of cervical lateral mass and facet fractures

4 patterns identified in lateral mass and facet fractures[203] are shown in *Table 28-32*.

Anterior subluxation of the fractured vertebra was observed in 77% of whole lateral-mass fractures[203].

Horizontal facet or separation fracture of the articular mass: Extension combined with compression and rotation may produce fracture of one pedicle and ipsilateral lamina which permits the detached articular mass ("floating" lateral mass) to rotate forward to a more horizontal orientation[204] (**horizontalization** of the facet) (*see Table 28-32*). May be associated with rupture of the anterior longitudinal ligament (ALL) and fissure of the disc at one or two levels. Neuro deficit is common. Unstable.

Table 28-32 Clasification of cervical lateral mass & facet fractures[203]

Designation	Diagram	Description
separation fracture		fractures through lamina and ipsilateral pedicle. Permits horizontalization of facet[204] (*see text*)
comminuted fracture		multiple fractures. Often associated with lateral angulation deformity
split fracture		coronally oriented vertical fracture in 1 lateral mass, with invagination of the superior articular facet of the level below
traumatic spondylolysis		bilateral horizontal fractures through pars interarticularis, separating anterior spinal elements from posterior

Failure of nonoperative treatment

A study of CT scans of 26 unilateral cervical facet fractures[205] identified the risk factors shown below for failure of nonoperative treatment (*see Figure 28-8* for illustration of the measurement definitions): where the fracture fragment **(FF)** height was defined as the maximum tip-to-tip cephalocaudal height on sequential sagittal reconstructions.

Nonoperative management is likely to fail if FF is:

1. **> 1 cm**, or
2. **> 40% of LM** (the height of the intact contralateral lateral mass at the same level, defined as the maximum tip-to-tip cephalocaudal height on sequential sagittal reconstructions)

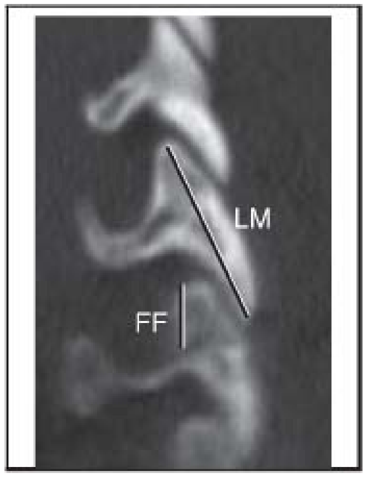


Figure 28-8 Facet fracture fragment measurements. Sagittal reconstructed CT. **FF** = fracture fragment height, **LM** = lateral mass height (measured on the contralateral side at the same level as the fracture, (not as shown here which just illustrates the technique used to measure LM)

Surgical treatment of cervical lateral mass & facet fractures

Most cases can be treated with a posterior approach using fixation screws (lateral mass screws or pedicle screws[203]) and rods extending at least 1 level above and below the level of fracture (usually omitting a screw on the side of the fracture at the index level). Simultaneous neural decompression is performed when needed. Additional treatment with an anterior approach may be required for release of rigid deformity or for additional anterior column support[203]. Some separation fractures may be candidates for osteosynthesis (to preserve motion) using a cervical pedicle screw[203] that traverses the fracture.

An anterior approach is an alternative. Advantage: usually only 1 level needs to be fused. Disadvantages: decompression of compressing fragments cannot always be accomplished and requires disrupting an area that may not be compromised (if there is subluxation, the anterior column is probably compromised).

28.6.6.1. Treatment of subaxial cervical spine fractures

MANAGEMENT OVERVIEW

Management of some types of C-spine fractures is covered in the preceding sections. For injuries not specifically addressed, general management principles

are as follows[1]:

1. immobilize and reduce externally (if possible): may use traction **x** 0-7 days
2. determine if there is an indication for decompression as soon as practical (clinical conditions permitting), and decompress if needed. Although controversial, the following are generally accepted indications for acute decompression in patients *without* complete spinal cord injury:
   A. radiographic evidence of bone or foreign material in the spinal canal with associated spinal cord symptoms
   B. complete block on CT, myelogram or MRI
   C. clinical judgement: e.g. a progressive incomplete spinal cord injury where the surgeon believes that decompression would be beneficial
3. ascertain stability of the injury (*see page 969*)
   A. stable fractures: treat in non-halo orthosis for 1-6 weeks (*see page 979*)
   B. unstable fractures: all of the following choices are appropriate, with little evidence to recommend one scheme over another in most cases
      1. traction **x** 7 weeks, followed by orthosis **x** 8 weeks
      2. halo **x** 11 weeks, followed by orthosis **x** 4 weeks
      3. surgical fusion, followed by orthosis **x** 15 weeks
      4. surgical fusion with internal immobilization (lateral mass screws & rods…) ± orthosis for short period of time (≈ several weeks)

SURGICAL TREATMENT

IN PATIENTS WITH COMPLETE SPINAL CORD LESIONS

Operating on a patient with a complete cord injury does not result in significant recovery of neurologic function[147]. However, aggressive non-surgical reduction of traumatic subluxation should be pursued.

The primary goal of surgery in this setting is spinal stabilization, allowing the patient to be placed in a sitting position for improved pulmonary function, for psychological benefit, and to allow initiation of rehabilitation. Although the spine will fuse spontaneously in many cases (taking ≈ 8-12 weeks), surgical stabilization expedites the mobilization process and reduces the risk of delayed kyphotic angulation deformity. Early surgery may lead to further neurological injury, and should be delayed until the patient has stabilized medically and neurologically. In most cases, performing surgery within 4-5 days (if the patient

is otherwise stable) is probably early enough to help reduce pulmonary complications.

In patients with incomplete lesions

Patients with incomplete cord injuries who have compromise of the spinal canal (by bone, disc, unreducible subluxation or hematoma) and either do not improve with nonoperative therapy or deteriorate neurologically should undergo surgical decompression and stabilization[147]. This may facilitate some further return of spinal cord function. An exception may be the central cord syndrome (*see page 948*).

ANTERIOR OR POSTERIOR?

The choice of technique depends to a large degree on the mechanism of injury, as the treatment should tend to counteract the instability, and ideally should not compromise structures that are still functioning. Instrumentation (wires/cables, lateral mass screws & rods, clamps…) immobilize the area of instability while bony fusion is occurring. In the absence of bony fusion, all mechanical devices will eventually fail, and so it becomes a "race" between fusion and instrument failure. Extensive injuries (including teardrop fractures (*see page 970*) and compression burst fractures) may require a combined anterior and posterior approach (staged, or in a single sitting; anterior decompression precedes posterior fusion).

Posterior immobilization and fusion

Indications: The procedure of choice for most flexion injuries. Useful when there is minimal injury to the vertebral bodies and in the absence of anterior compression of the spinal cord and nerves. Including: posterior ligamentous instability, traumatic subluxation, unilateral or bilateral locked facets, simple wedge compression fractures.

The most common technique consists of open or closed reduction, followed by lateral mass screws & rods (*see page 179*). Interlaminar Halifax clamps are an alternative[206]. Although successes have been reported using methylmethacrylate[207], it does not bond to bone and weakens with age, and thus its use in the setting of traumatic injury is discouraged[208].

Choice of posterior technique: If the anterior column is capable of weight-bearing and the posterior elements are not damaged or absent, wiring and fusion provides adequate stability. If the anterior weight-bearing column is significantly

damaged, or if there is absence or compromise of the lamina or spinous processes, then either a combined anterior-posterior approach is needed or posterior rigid instrumentation (e.g. lateral mass screw-plate or rod fixation) with fusion is recommended[209].

ANTERIOR APPROACH

Does not depend on integrity of posterior elements to achieve stability.

Indications:

1. fractured vertebral body with bone retropulsed into spinal canal (burst fracture)
2. most <u>extension</u> injuries
3. severe fractures of posterior elements that preclude posterior stabilization and fusion
4. may be used for traumatic subluxation of the cervical spine

Usually consists of:

1. corpectomy: decompresses the neural elements (if necessary) and removes fractured and structurally compromised bone
   A. decompression usually requires wide corpectomy, at least ≈ 16 mm (palpate anterior surface of vertebral body to determine width; note position of vertebral arteries on pre-op CT). NB: it is suggested to take the corpectomy no wider than 3 mm lateral to the medial edge of the longus coli muscle, this leaves ≈ 5 mm margin of safety to the foramen transversarium[210]
   B. if decompression is not needed, ≈ 12 mm corpectomy suffices (i.e. about the width of a half-inch cottonoid)

   AND
2. strut graft fusion: replaces the involved body or bodies with either:
   A. bone (usually iliac crest, rib or fibula, either homologous or cadaveric)
   B. or synthetic cage (e.g. titanium or PEEK)
3. usually accompanied with compression plates
4. usually followed with external immobilization

COMPLICATIONS OF SURGICAL TREATMENT

1. hardware problems
   A. wire failure
      1. improper wire gauge for type of fracture

2. improper wire-handling
3. inadequate post-operative immobilization
   a. improper brace selected
   b. poor patient compliance with immobilization device

B. problems with plating
1. screw pull-out, loosening or breakage
2. fatigue fracture of plate
3. screw injury: nerve root, spinal cord or vertebral artery

2. failure of graft to take (nonunion)
3. judgmental error
   A. failure to incorporate all unstable levels
   B. improper surgical approach

CERVICAL BRACING

COLLARS

Soft (sponge rubber) collar: does not immobilize the cervical spine to any significant degree. Its function is primarily to remind the patient to reduce neck movements.

Rigid cervical collars

Inadequate for stabilizing upper and mid-cervical spine and for preventing rotation. Common rigid collars:

- Miami J collar & Aspen collar: have removable pads
- **Philadelphia collar**: no removable pads. Feels hotter to wear

POSTER BRACES

Distinguished from cervicothoracic orthoses (*see below*) by the lack of straps under the axilla. Includes the four poster brace. Generally good for preventing flexion at midcervical levels.

CERVICOTHORACIC ORTHOSES

Cervicothoracic orthoses **(CTO)** incorporate some form of body vest to immobilize the cervical spine. The following are presented in increasing degree of immobilization.

Guilford brace: essentially a ring around the occiput and chin connected by

two posts to anterior and posterior thoracic pads.

SOMI brace: acronym for Sternal Occipital Mandibular Immobilizer. Good for bracing against flexion (especially upper cervical spine). Inadequate for hyperextension type injuries because of weak occipital support. Has special forehead attachment to allow patient to eat comfortably without mandibular support.

"**Yale brace**": a sort of extended Philadelphia collar. The most effective CTO for bracing against flexion-extension and rotation. Major shortcoming is poor prevention of lateral bending (only ≈ 50% reduced).

HALO-VEST BRACE

Can immobilize the upper or lower cervical spine, not very good for mid-cervical spine (due to snaking of the midcervical spine). Unable to provide adequate distraction support following vertebral body resection when patient assumes upright position (i.e. it is not a portable cervical traction device). Overall reduction of flexion/extension as well as lateral bending is ≈ 90-95%, rotation is reduced by 98%. For placement, *see page 942*.

FOLLOW-UP SCHEDULE

After initial management (surgical or nonsurgical) of cervical spine problems (stable or unstable) the follow-up schedule shown in *Table 28-33* is suggested to permit recognition of problems in time for treatment[1].

Table 28-33 Sample follow-up cervical spine clinic visit schedule

Time post-op	Agenda
7-10 d	(for post-op patients only) wound check, D/C sutures/staples if used
6 wks	AP & lateral C-spine x-ray in brace
3 months	• AP & lateral C-spine x-rays with flexion/extionsion views out of brace • if x-rays look good and patient is doing well, begin weaning brace
6 months	• AP & lateral C-spine x-rays with flexion/extionsion views • some surgeons release patients at this time if they are doing well
1 year (optional)	• AP & lateral C-spine x-rays with flexion/extionsion views • release patient if they are doing well

28.6.7. Sports related cervical spine injuries

Any of the previously described injuries can be sports related. This section considers some injuries peculiar to sports. Also *see page 850* for sports-related

head injuries.

Bailes et al.[211] classified sports-related spinal cord injures **(SCI)** as shown in *Table 28-34*. Type II injuries include spinal concussion, spinal neuropraxia (*see below*), and the burning hands syndrome (*see below*), all in the absence of radiographic abnormalities and all with complete resolution of symptoms. Patients should be carefully evaluated, and return to competition should not be allowed in the presence of neurologic deficit, radiographically demonstrated injury, certain congenital C-spine abnormalities, and possibly for “repeat offenders” (see *Return to play and pre-participation guidelines* below). Type III injuries are the most common. Unstable injuries should be treated appropriately (*see page 977*).

Table 28-34 Sports-related spinal cord injuries

Type	Description
I	permanent SCI
II	transient SCI without radiographic abnormality
III	radiologic abnormality without neurologic deficit

FOOTBALL-RELATED CERVICAL SPINE INJURIES

Football players with suspected C-spine injury should not have their helmet removed in the field (*see page 934*). The following terms probably originated as locker-room jargon for various cervical spine-related injuries usually sustained in playing football. Medical definitions have subsequently been retro-fitted to them. As a result, the precise definitions may not be uniformly agreed upon. Although the semantics may differ, it is more important from a diagnostic and therapeutic standpoint to distinguish nerve root injuries, brachial plexus injuries, and spinal cord injuries.

1. **cervical cord neuropraxia** 212 **(CCN)**: sensory changes which may involve numbness, tingling or burning. May or may not be associated with motor symptoms of weakness or complete paralysis. Typically lasts < 15 mins (although may persist up to 48 hrs), involves all 4 extremities in 80%. Narrowing of the sagittal diameter of the cervical spinal canal is felt to be contributory. With resumption of contact activities, recurrence rate is ≈ 56%, with higher risks of recurrence among those with narrower canals. Evaluation should include cervical MRI. Torg[212] feels that uncomplicated cases of CCN (no spinal instability and no MRI evidence of cord defect or edema) have a low risk of permanent injury and does not recommend

activity restrictions

2. "**stinger**" or "**burner**": distinct from the burning hands syndrome. Unilateral. Burning dysesthetic pain radiating down one arm from the shoulder, sometimes associated with weakness involving the C5 or C6 nerve roots. Usually follows a tackle. May result from downward traction on the upper trunk of the brachial plexus or by direct nerve root compression in the neural foramina (not a SCI)
3. **burning hands syndrome** 213: similar to a stinger, but bilateral. Probably represents a SCI (possibly a mild variant of a central cord syndrome, *see page 948*)
4. other neurologic injuries include: vascular injury to carotid or vertebral arteries. Usually related to intimal dissection (*see page 1160*) following a direct blow to the neck or by extreme movements. Symptoms are those of a TIA or stroke

Spear tackler's spine

Rule changes in 1976 banned spearing (the practice of using the football helmet as a battering ram to tackle an opponent) and resulted in a reduction of the number of foot-ball-related occurrences of cervical spine fractures and quadriplegia[214].

Four characteristics of spear tackler's spine:

1. cervical spinal stenosis
2. loss of normal cervical lordosis
3. evidence of pre-existing traumatic abnormalities
4. documented spear-tackler's technique

Suggested management:

The athlete is removed from competition until the cervical lordosis returns and the player learns to use other tackling techniques.

RETURN TO PLAY AND PRE-PARTICIPATION GUIDELINES

Return to play **(RTP)** and pre-participation evaluation guidelines related to the cervical spine are shown in *Table 28-35* (modified[215]). These are just guidelines, and do not insure safety. Clinical judgement must always be employed.

Table 28-35 C-spine-related contraindications for participation in contact sports*

Condition[†]	C.I.[‡]
Congenital[§]	
1. odontoid abnormalities (serious injury may result from atlanto-axial instability)	
A. complete aplasia (rare)	absolute
B. hypoplasia (seen in conjunction with achondroplasia and spondyloepiphyseal dysplasia)	absolute
C. os odontoideum (probably of traumatic origin)	absolute
2. atlanto-occipital fusion (partial or complete fusion of atlas to occiput): sudden onset of symptoms & sudden death have been reported	absolute
3. Klippel-Feil anomaly (congenital fusion of 2 or more cervical vertebrae)[Δ]	
A. Type I: mass fusion of C-spine to upper T-spine	absolute
B. Type II: fusion of only 1 or 2 interspaces	
1. associated with limited ROM, occipitocervical anomalies, instability, disc disease or degenerative changes	absolute
2. associated with full ROM and none of the above	none
Acquired	
1. cervical spinal stenosis[¶]	
A. asymptomatic	none
B. with one episode of cord neuropraxia	relative
C. cord neuropraxia + MRI evidence of cord defect or edema	absolute
D. cord neuropraxia + ligamentous instability, symptoms or neurologic findings > 36 hrs, or multiple episodes	absolute
2. spear tackler's spine (*see text*)	absolute
3. spina bifida occulta: rare, incidental x-ray finding	none
Post-traumatic upper cervical spine	
1. atlantoaxial instability (ADI > 3 mm adults, > 4 mm peds)	absolute
2. atlantoaxial rotatory fixation (may be associated with disruption of transverse ligament)	absolute
3. fractures	
A. healed, pain-free, full ROM, & no neurologic findings with any of the following fractures: nondisplaced Jefferson fracture; odontoid fracture; or lateral mass fracture of axis	none
B. all others	absolute
4. post-surgical atlantoaxial fusion	absolute
Post-traumatic subaxial cervical spine	
1. ligamentous injuries: > 3.5 mm subluxation, or > 11° angulation on flexion-extension views	absolute
2. fractures	
A. healed, stable fractures listed here with normal exam: VB compression fracture without posterior involvement; spinous process fractures	none
B. VB fractures with sagittal component or posterior bony or ligamentous involvement	absolute
C. comminuted fracture with displacement into spinal canal	absolute
D. lateral mass fracture producing facet incongruity	absolute
3. intervertebral disc injury	
A. healed herniated disc treated conservatively	none
B. S/P ACDF with solid fusion, no symptoms, normal exam and full pain-free ROM	none

C. chronic herniated disc with pain, neuro findings or ↓ ROM, or acute herniated disc	absolute
4. S/P fusion	
A. stable one-level fusion	none
B. stable two-level fusion	relative
C. fusion > 2 levels	absolute

* organized contact sports includes[215]: boxing, football, ice hockey, lacrosse, rugby & wrestling

† also *see* *page 851* for cranial-related (and craniocervical) conditions (e.g. Chiari I malformation…)

‡ C.I. = contraindications, classified as absolute, relative (i.e. uncertain) or none

§ congenital abnormalities may have particular relevance to *Special Olympics*

Δ NB: Klippel-Feil may be associated with abnormalities in other organ systems (e.g. cardiac) which may impact on participation in contact sports (*see* *page 253*)

¶ Pavlov ratio (*see* *page 489*) has a low positive predictive value for injuries in contact sports and is therefore not a useful screening test (i.e. an asymptomatic Pavlov ratio < 0.8 is not a contraindication to participation)

28.6.8. Delayed cervical instability

Definition (adapted[216]): cervical instability that is not recognized until beyond 20 days after the injury. The instability itself may be delayed, or the recognition may be delayed. Reasons for delayed cervical instability:

1. inadequate radiologic evaluation[47]
   A. incomplete studies (e.g. must see all the way to C7-T1 junction)
   B. suboptimal studies: motion artifact, incorrect positioning… Etiologies include: poor patient cooperation as a result of agitation/intoxication, portable films, poor technique…
2. abnormality missed on x-ray
   A. overlooked fracture, subluxation
   B. injury failed to be demonstrated despite sufficiently adequate x-rays[216A]

A. *see* *page 939* for recommendations of extent of radiologic workup

1. type of fracture not demonstrated on the radiographs obtained
2. patient positioning (e.g. supine) may reduce some malalignment
3. spasm of cervical muscles may reduce and/or stabilize the injury
4. microfractures

3. inadequate models: some findings may be judged to be stable using certain models, but in the long-run may be unstable (there is no perfect model for instability)

Further studies or repeat x-rays several weeks post-trauma should be considered with neurologic deficit, persistent pain, significant degenerative changes when the original films were suboptimal, subluxations < 3 mm, or when surgery is contemplated[217].

28.7. Blunt cerebrovascular injuries

Cerebrovascular injuries may be classified as follows:

1. penetrating injury: *see page 998*
2. nonpenetrating injury: discussed in this chapter (*see below*)
   A. blunt trauma: <u>dissection</u> is the usual type of injury
   B. stretch: e.g. dissection from spinal manipulation or neck hyperextension
   C. occlusion by bone: more common with vertebral arteries
      1. kinking: e.g. with facet dislocation
      2. compression by bone fragments: e.g. by fractures through foramen transversarium
3. iatrogenic injuries may be related to angiography catheters

The material that follows deals with nonpenetrating cerebrovascular injuries (mostly blunt trauma).

Incidence of blunt cerebrovascular injury **(BCVI)** in the literature: 1-2% of blunt trauma patients[218] (among those who stayed > 24 hrs in a trauma hospital the incidence was 2.4%[218]). Optimal screening, diagnostic and treatment methods are controversial. Improving experience with CTA & endovascular techniques is resulting in a reworking of paradigms. A 13% mortality rate is considered low. Nearly one-third of cases are not treatable.

Risk factors

Risk factors for BCVI are shown in *Table 28-36*. However, BCVI can occur even in the absence of identifiable risk factors[218].

Presentation

Signs and symptoms of BCVI are shown in *Table 28-37*.

Table 28-36 Risk factors for BCVI[219]

• high energy transfer mechanism associated with:
• displaced mid face fracture (LeForte fracture type II or III - *see page 890*) • basilar skull fracture involving carotid canal
• TBI consistent with DAI and GCS < 6
• cervical vertebral body or transverse foramen fracture, subluxation, or ligamentous injury at any level
• any fracture involving C1-3
• near hanging with anoxic brain injury
• clothesline-type injury or seat belt abrasion with significant cervical swelling, pain, or mental status changes

Table 28-37 Signs & symptoms of BCVI[219]

• arterial hemorrhage from neck/nose/mouth (? go to O.R.)
• cervical bruit in pt. < 50 yrs old
• expanding cervical hematoma
• focal neurologic deficit: TIA, Horner's syndrome, hemiparesis, VBI (*see page 1158*)
• neurologic deficit inconsistent with head CT
• stroke on CT or MRI

Approach

The following is a summary of the Western Trauma Association[219] guidelines. Their recommendations are based on observational studies and expert opinion (no Class I data was available).

Evaluation of patients with risk factors or signs/symptoms of BCVI

1. 16-slice multidetector CT angiography **(MDCTA)**[A] should be obtained as follows
   A. emergently in patients with signs/symptoms of BCVI (*see Table 28-37*)
   B. asymptomatic patients with risk factors (*see Table 28-36*) for BCVI:
      1. if the presence of BCVI would alter therapy (e.g no contraindication to heparin) then MDCTA should be done within 12 hours if possible
      2. if heparin is contraindicated due to associated injuries, timing of MDCTA is determined by patient stability

2. if the MDCTA is equivocal, or if it is negative but clinical suspicion remains high: a catheter arteriogram should be done (otherwise, if negative: stop)
3. **grading**: if the MDCTA or the arteriogram shows positive findings (listed on *page 1162*):
   A. the injury is graded using the scale shown in *Table 28-38*[225] (sometimes referred to as the "Denver grading scale")
   B. proceed with grade-based management (*see below*)

Table 28-38 BCVI grading scale[225]

Grade	Description
I	luminal irregularity with < 25% stenosis
II	≥ 25% luminal stenosis or intraluminal thrombus or raised intimal flap
III	pseudoaneurysm
IV	occlusion
V	transection with free extravasation

Management of documented BCVI

1. grade specific therapy
   - Grade I
     1. heparin as outlined (*see below*)
     2. stroke rate is so low with Grade I that surgery is not justified
   - Grade II-IV:
     1. administer heparin as outlined (*see below*)
     2. if available, consultation with neuroendovascular interventionalist or vascular neurosurgeon to assess for intervention:
        a. surgically accessible lesions in patients without complete stroke: pursue operative repair
        b. inaccessible lesions[B]: consider endovascular repair
   - Grade V: highly lethal injury
     1. accessible lesions should be considered for urgent surgical repair (anecdotal)
     2. inaccessible lesions (the majority): incomplete transection may be amenable to endovascular stenting with concurrent antithrombotics; complete transections should be ligated (or occluded endovascularly)

2. repeat MDCTA or angiography **7-10 days post injury** to assess healing[226]. Results:
   A. lesion healed: discontinue anticoagulation
   B. non-healed lesions:
      1. consider endovascular stenting "with caution" for severe luminal narrowing or expanding pseudoaneurysm (controversial: results have been mixed - favorable[227] and unfavorable[228])
      2. transition from heparin to aspirin (75-150 mg/d) alone
      3. repeat MDCTA or angiography 3 months post injury (rationale: most heal with canalization in 6 wks). Results:
         a. healed lesion: consider discontinuing aspirin
         b. non-healed: optimal drug and duration is not known. Recommendation[219]: lifelong antiplatelet therapy with either aspirin or clopidogrel. Dual therapy is used for acute coronary syndromes and following angioplasty (± stenting) but is not recommended in patients who have had a stroke or TIA[229]

A. CTA on scanners with ≥ 16 detectors have an accuracy near 99%[220] & equivalent predictive value to cerebral angiogram. MRA[221], [222] and ultrasound[223], [224] are not considered adequate for BCVI screening

B. most inaccessible lesions are at the skull base

Heparinization: When anticoagulation is not contraindicated[A], perform a baseline PTT and then begin heparin drip 15 U/kg/hr IV. Repeat PTT after 6 hours, and titrate to PTT = 40-50 seconds.

A. trauma contraindications to heparinization: patients that are actively bleeding, have potential for bleeding, or in whom the consequences of bleeding are severe. Specific examples include: liver and spleen injuries, major pelvic fractures, and intracranial hemorrhage

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Dissection-related anticoagulation risks include: extension of the medial hemorrhage (with possible SAH), and intracerebral hemorrhage (conversion of pale infarct to hemorrhagic).

CAROTID ARTERY BLUNT INJURIES

For general information related to cerebral arterial dissections and for spontaneous dissections, *see page 1160*. For evaluation and management, *see above*.

This section considers blunt (i.e. nonpenetrating) specifically related to ICA dissection. Neck hyperextension with lateral rotation is a common mechanism of injury, and is thought to stretch the ICA over the transverse processes of the upper cervical spine. In posttraumatic dissection, ischemic symptoms are the most common[230]. Post-traumatic dissections may follow minor injuries to already susceptible vessels, e.g. in a patient with fibromuscular dysplasia.

Etiologies:

1. following MVAs: the most common etiology
2. attempted strangulation[231]
3. spinal manipulation therapy: VA dissections are more common than ICA

Most carotid dissections start ≈ 2 cm distal to the ICA origin.

Clinical

The risk of stroke with various ICA dissection grades is shown in *Table 28-39*

Grade I injuries: 70% heal with or without heparin. 25% will persist. 4-12% will progress to more severe grade. Data suggests that anticoagulation reduces the risk of progression[232].

Grade II: ≈ 70% progress to more severe grade even with heparin therapy.

Grade III & IV: most persist.

Initially, there may be no neurologic sequelae, however, progressive thrombosis, intramural hemorrhage or embolic phenomenon may develop in a delayed fashion. The distribution of time delays following trauma to time of presentation are shown in *Table 28-40* (the majority are evident within the 1st 24 hours).

Table 28-39 Risk of stroke with ICA dissection

Grade*	Description	Stroke risk
I	stenosis < 25%	3%
II	stenosis > 25%	11%
III	pseudoaneurysm	44%
IV	occlusion	uniformly lethal

* for grading, *see Table 28-38*

Table 28-40 Time to presentation after non-penetrating trauma

Time	%
0-1 hours	6-10% of cases
1-24 hours	57-73%
after 24 hours	17-35%

MANAGEMENT

See *Management of documented BCVI* on page 983.

OUTCOME

Natural history is not well known. Many patients with minor symptoms may not present and presumably do well. In one series, 75% of patients returned to normal, 16% had a minor deficit, and 8% had a major deficit or died[233].

VERTEBRAL ARTERY BLUNT INJURIES

PRACTICE GUIDELINE 28-20 VERTEBRAL ARTERY BLUNT INJURIES

Diagnosis

Level III[234]: conventional angiography or MRA* after nonpenetrating cervical trauma in patients who have: complete SCI, fracture through the foramen transversarium, facet dislocation, and/or vertebral subluxation

Treatment

Level III[234]

- recommended: anticoagulation with IV heparin for vertebral artery injury **(VAI)** with evidence of posterior circulation *stroke*
- recommended: either observation or treatment with anticoagulation for VAI with evidence of posterior *ischemia*
- recommended: observation for VAI with no evidence of either of above

* at the present time, MDCTA would probably be recommended over MRA for this indication (editor)

Blunt vertebral artery injury **(BVI)** is very rare, being found in 0.5-0.7% of

patients with blunt injuries using aggressive screening[235]. It may produce vertebrobasilar insufficiency **(VBI)**. Fractures through the foramen transversarium, facet fracture-dislocation, or vertebral subluxation are frequently identified in patients with BVI[232, 236, 237] (overall incidence increases to 6% in the presence of cervical fracture or ligamentous injury[235]).

Etiologies

While motor vehicle accidents are the most common mechanism of injury, any trauma that can injure the C-spine can cause BVI (diving accidents, spinal manipulation…).

1. automobile accidents
2. spinal manipulation therapy **(SMT)**: including chiropractic[238] or similar, which comprise 11 of 15 case reports reviewed by Caplan, et al.[239]). VA dissections were independently associated with SMT within 30 days in multivariate analysis (odds ratio = 6.62, 95% CI 1.4 to 30)[240]
3. sudden head turning
4. direct blows to the back of the neck[239]

Stroke from BVI

Risk of stroke is shown in *Table 28-41*[232]. Unlike with carotid injuries, there is rarely a premonitory "warning" TIA. Time from injury to stroke: mean 4 days (range: 8 hours -12 days).

Evaluation

Indications: associated C-spine injuries are common and are the only independent predictor of BVI - no fracture pattern stands out as being more commonly associated. Grading: see *Table 28-38*.

When BVI is identified, it is critical to assess the status of the contralateral VA.

Table 28-41 Risk of stroke with VA injuries

Grade*	Description	Stroke risk
I	stenosis < 25%	19%
II	stenosis > 25%	40%
III	pseudoaneurysm	13%

IV	occlusion	33%

* for grading, see Table 28-38 (no grade V patients in this study)

Treatment

Although there may be some differences from carotid dissections, the management outlined above (*see page 983*) is suggested. Strokes were more frequent in patients with BVI who were not treated initially with IV heparin despite an asymptomatic BVI[232]. However, based on historical controls, it is not clear if either screening or treatment improves overall outcome[235].

Treatment options include endovascular stenting when amenable. This can restore near-normal flow, but long-term results are lacking[241]. Also, stenting requires ≥≈3 months of antiplatelet therapy which is contraindicated in some situations.

Outcome

Overall mortality with BVI was 16% (7/44)[235]. Bilateral VA dissection appears highly fatal.

28.8. Thoracic & lumbar spine fractures

BIOMECHANICS

Thoracolumbar junction **(TLJ)**: comprised of T11, T12 & L1: normally has a slight lordosis of ≤ 10°. 64% of spine fractures occur at the TLJ, usually T12-L1. 70% of these occur without immediate neurologic injury.

For measurements of normal kyphosis, see *Sagittal balance*, page 441.

28.8.1. Assessment and management decisions

A widely used model for thoracolumbar spine stability is the 3-column model of Denis (*see below*). A recently proposed TLICS system is presented on *page 990*.

THREE COLUMN MODEL

Denis' 3 column model of the spine (*see Figure 28-9*) attempts to identify CT criteria of instability of thoracolumbar spine fractures[242]. This model has generally good predictive value, however, any attempt to create "rules" of instability will have some inherent inaccuracy.

1. **anterior column**: anterior half of disc and vertebral body **(VB)** (includes anterior anulus fibrosus **(AF)**) plus the anterior longitudinal ligament **(ALL)**
2. **middle column**: posterior half of disc and vertebral body (includes posterior wall of vertebral body and posterior AF), posterior longitudinal ligament **(PLL)**, & the pedicles
3. **posterior column**: posterior bony complex (posterior arch) with interposed posterior ligamentous complex (supraspinous and interspinous ligament, facet joints and capsule, and ligamentum flavum **(LF)**). Injury to this column alone does not cause instability

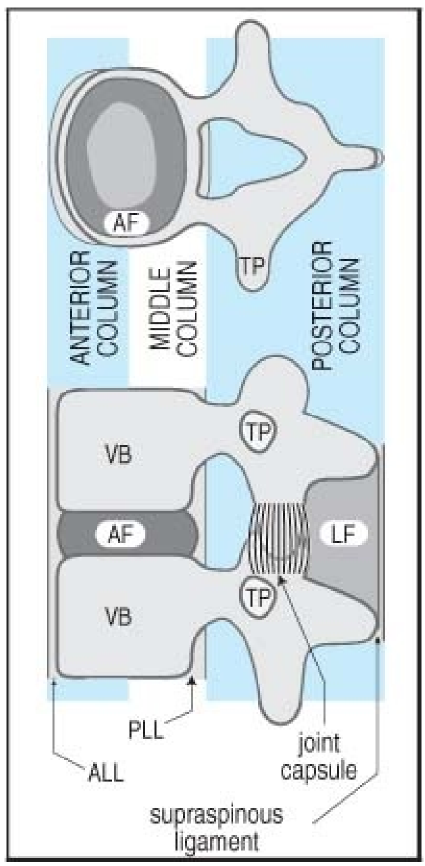


Figure 28-9 Three column model of the spine (TP = transverse process, see text for other abbreviations) (Adapted from Spine, Denis F, Vol. 8, pp. 317-31, 1983, with permission)

CLASSIFICATION INTO MAJOR & MINOR INJURIES

Minor injuries

Involve only a part of a column and do not lead to acute instability (when not accompanied by major injures). Includes:

1. fracture of transverse process: usually neurologically intact except in two areas:
   A. L4-5 → lumbosacral plexus injuries (there may be associated renal injuries, check U/A for blood)
   B. T1-2 → brachial plexus injuries
2. fracture of articular process or pars interarticularis
3. isolated fractures of the spinous process: in the TL spine: these are usually due to direct trauma. Often difficult to detect on plain x-ray
4. isolated laminar fracture: rare. Should be stable

Major injuries

The McAfee classification describes 6 main types of fractures[243]. A simplified system with four categories follows (also *see Table 28-42*):

1. **compression fracture**: compression failure of anterior column. Middle column <u>intact</u> (unlike the 3 other major injuries below) acting as a fulcrum,
   A. 2 subtypes:
      1. anterior: most common between T6-T8 and T12-L3
         a. lateral x-ray: wedging of the VB anteriorly, no loss of height of posterior VB, no subluxation
         b. CT: spinal canal intact. Disruption of anterior end-plate
      2. lateral (rare)
   B. clinical: no neurologic deficit

Table 28-42 Column failure in the four major types of thoracolumbar spine injuries*

Fracture type	Column		
	Anterior	Middle	Posterior
compression	compression	intact	intact, or distraction if severe
burst	compression	compression	intact
seat-belt	intact or mild compression of 10-20% of anterior VB	distraction	
fracture-dislocation	compression, rotation, shear	distraction, rotation, shear	

* adapted[242] with permission

2. **burst fracture**: pure axial load → compression of vertebral body → compression failure of anterior and middle columns. Occur mainly at TL junction, usually between T10 and L2
   A. 5 subtypes (L5 burst fractures may constitute a rare subtype, *see page 990*)
      1. fracture of both end-plates: seen in lower lumbar region (where axial load → increased extension, unlike T-spine where axial load → flexion)
      2. fracture of superior end-plate: the most common burst fracture. Seen at TL junction. Mechanism = axial load + flexion
      3. fracture of inferior end-plate: rare
      4. burst rotation: usually midlumbar. Mechanism = axial load + rotation
      5. burst lateral flexion: mechanism = axial load + lateral flexion
   B. radiographic evaluation
      1. lateral x-ray: cortical fracture of posterior VB wall, loss of posterior VB height, retropulsion of bone fragment from end plate(s) into canal
      2. AP x-ray: increase of interpediculate distance **(IPD)**, vertical fracture of lamina, splaying of facet joints: ↑ IPD indicates failure of middle column
      3. CT: demonstrates break in posterior wall of VB with retropulsed bone in spinal canal (average: 50% obstruction of canal area), increase in IPD with splaying of posterior arch (including facets)
      4. MRI or myelogram: anterior encroachment in spinal canal
   C. clinical: depends on level (thoracic cord more sensitive and less room in canal than conus region), the impact at the time of disruption, and the extent of canal obstruction
      - ≈ 50% intact at initial examination (half of these recalled leg numbness, tingling, and/or weakness initially after trauma that subsided)
      - of patients with deficits, only 5% had complete paraplegia
3. **seat-belt fracture**[A]: flexion across a fulcrum anterior to the anterior column (e.g. seat belt) → compression of anterior column & distraction failure of both middle and posterior columns. May be bony or ligamentous
   A. 4 subtypes
      1. **Chance fracture**: one level, totally through bone
      2. one level, through ligaments

3. two level, through bone in middle column, through ligament in anterior and posterior columns
4. two level, through ligament in all 3 columns

B. radiographic evaluation
1. plain x-ray: ↑ interspinous distance, pars interarticularis fractures, and horizontal split of pedicles and transverse process. No subluxation
2. CT: axial cuts are poor for this type (most of fracture is in plane of axial CT cuts). Sagittal and coronal reconstructions demonstrate this well. May demonstrate pars fracture

C. clinical: no neurologic deficit

4. **fracture-dislocation**: failure of all 3 columns due to compression, tension, rotation or shear → subluxation or dislocation
A. x-ray: occasionally, may be reduced when imaged. Look for other markers of significant trauma (multiple rib fractures, unilateral articular process fractures, spinous process fractures, horizontal laminar fractures)
B. 3 subtypes
1. flexion rotation: posterior and middle columns totally ruptured, anterior compressed → anterior wedging
a. lateral x-ray: subluxation or dislocation. Preserved posterior VB wall. Increased interspinous distance
b. CT: rotation and offset of VBs with ↓ canal diameter. Jumped facets
c. clinical: 25% neurologically intact. 50% of those with deficits were complete paraplegics
2. shear: all 3 columns disrupted (including ALL)
a. when trauma force directed posteriorly to anteriorly (more common) VB above shears forward fracturing the posterior arch (→ free floating lamina) and the superior facet of the inferior vertebra
b. clinical: all 7 cases were complete paraplegics
3. flexion distraction
a. radiographically resemble seat-belt type with addition of subluxation, or with compression of anterior column > 10-20%
b. clinical: neurologic deficit (incomplete in 3 cases, complete in 1)

A. some call this a flexion-distraction fracture, but that term is also used for a subtype of fracture-

dislocation

Associated injuries

In addition to the above, associated injuries include: vertebral end-plate avulsion, ligamentous injuries, and hip and pelvic fractures. Thoracolumbar fractures may be associated with hemodynamic instability as a result of hemothorax or aortic injury. Fractures of the transverse processes may be associated with abdominal trauma (e.g renal injuries at L4-5).

STABILITY AND TREATMENT OF THORACOLUMBAR SPINE FRACTURES

Minor injuries

Isolated thoracolumbar transverse process fractures (as demonstrated on spinal CT) do not require intervention or consultation of a spine service[244, 245].

Major spine injuries

Denis categorized the instability as:

- 1st degree: mechanical instability
- 2nd degree: neurological instability
- 3rd degree: mechanical & neurological instability

Table 28-43 Treatment of stable anterior or middle column thoracolumbar spine injuries

- treat initially with analgesics and recumbency (bed-rest) for comfort **x** 1-3 weeks
- diminution of pain is a good indication to commence mobilization with or without external immobilization (corset or Boston brace or extension TLSO **x** ≈ 12 weeks) depending on the degree of kyphosis
- vertebroplasty (± kyphoplasty) may be an option (*see page 994*)
- serial x-rays to rule-out progressive deformity

Anterior column injury

Isolated anterior column injuries are usually stable and are treated as outlined in *Table 28-43*. The following exceptions may be unstable (1st degree) and often require surgery[242, 246]:

UNSTABLE COMPRESSION FRACTURE

1. a single compression fracture with:
   A. loss of > 50% of height with angulation (particularly if the anterior part of the wedge comes to a point)
   B. excessive kyphotic angulation at one segment[A] (various criteria are used, none are absolute. Values quoted: > 30°, > 40°)
2. 3 or more contiguous compression fractures
3. neurologic deficit (generally does not occur with pure compression fracture)
4. disrupted posterior column or more than minimal middle column failure
5. progressive kyphosis: risk of progressive kyphosis is increased when loss of height of anterior vertebral body is > 75%. Risk is higher for lumbar compression fractures than thoracic

A. usually indicates disruption of the posterior ligamentous complex

Middle column failure

Unstable (often requiring surgery) with the following exceptions which should be stable (stable injuries may be treated as outlined in *Table 28-43*):

STABLE MIDDLE COUMN Fx

1. above T8 if the ribs and sternum are intact (provides anterior stabilization)
2. below L4 if the posterior elements are intact
3. Chance fracture (anterior column compression, middle column distraction)
4. anterior column disruption with minimal middle column failure

Posterior column disruption

Not acutely unstable unless accompanied by failure of the middle column

(posterior longitudinal ligament and posterior anulus fibrosus). However, chronic instability with kyphotic deformity may develop (especially in children).

Seat-belt type injuries without neurologic deficit

No immediate danger of neurologic injury. Treat most with external immobilization in extension (e.g. Jewett hyperextension brace or molded TLSO).

Fracture-dislocation

Unstable. Treatment options:

1. surgical decompression and stabilization: usually needed in cases with
   A. compression with > 50% loss of height with angulation
   B. or, kyphotic angulation > 40° (or > 25%)
   C. or, neurologic deficit
   D. or, desire to shorten length of time of bedrest
2. prolonged bedrest: an option if none of the above are present

When vertebral body resection (vertebral corpectomy) is performed, options to access: transthoracic or transabdominal approach (or combined), transpedicular (for thoracic spine), lateral (retroperitoneal/retropleural) approach. Fracture and compression usually occurs at the superior margin of vertebral body, thus start resection at the inferior disc interspace. Followed by strut graft (cage or bone: iliac crest or fibula or tibia). Posterior instrumentation is usually required (see *Spinal instrumentation*, page 991).

Burst fractures

Some burst fractures may eventually cause neurologic deficit (even if no deficit initially). Middle column fragments in canal endanger the neuro elements. Criteria have been proposed to differentiate mild burst fractures from severe ones as follows[242, 247]:

BURST FRACTURE SURGICAL NDICATIONS

Surgery recommended for burst fracture with any of the following:

1. anterior vertebral body height ≤ 50% of the posterior height
2. residual canal diameter ≤ 50% of normal*
3. kyphotic angulation ≥ 20°

4. when the increased interpediculate distance usually present on the initial film widens further on AP x-ray when standing in brace/cast
5. neurologic deficit (incomplete)
6. progressive kyphosis

---

* retropulsed bone in the canal is often resorbed with either bracing or surgery and is therefore controversial as an isolated indication for surgery[248, 249]

For those not undergoing surgery (i.e. when surgery is not required or is contraindicated), an option is to treat with recumbency from 1-6 weeks[247]. Avoid early ambulation → further axial loading (even in cast). When appropriate, begin ambulation in an orthosis (e.g. molded thoracolumbar sacral orthosis **(TLSO)** or a Jewett brace) and follow patient for 3-5 months with serial x-rays to detect progressive collapse or angulation which may need further intervention. L5 burst fractures may be an exception to the usual management (*see below*).

L5 burst fractures: These fractures are extremely rare, and it is difficult for instrumentation to maintain alignment at this level[250]. Therefore, if neurologic deficit is absent or mild, conservative treatment should be considered[250, 251]. Regardless of treatment, patients will probably lose ≈ 15° of lordosis between L4 and the sacrum. Permanent neurologic loss may occur[251].

Early reports of conservative management utilized ≈ 6-10 weeks of bed rest followed by mobilization in a brace. A more contemporary approach utilizes 10-14 days of bed rest. The patient should be fitted with a TLSO with a unilateral non-movable thigh cuff in 10° of flexion (on either side, to reduce motion at the fracture segment). Mobilization should be done very gradually as the pain allows. The brace should be worn ≈ 4-6 months, and serial x-rays should be performed to rule-out progressive deformity.

If surgical treatment is indicated, a posterior approach with fusion and fixation of L4-S1 may be performed utilizing pedicle screws.

THORACOLUMBAR INJURY CLASSIFICATION AND SEVERITY SCORE (TLICS)

The TLICS system has been proposed to simplify classification and discussion of thoracolumbar fractures[252, 253]. Points are assigned as shown in *Table 28-44*. The scores are summed, and management guidelines are given in *Table 28-45*.

Neurologic deficit, especially when partial, favors surgery.

As of this writing, the TLICS system has not been validated.

Table 28-44 Thoracolumbar injury classification & severity score (TLICS)

Category	Finding	Points
Radiographic findings	compression fx	1
	burst component or lateral angulation > 15°	1
	distraction injury	2
	translational/rotational injury	3
Neurologic status	intact	0
	root injury	2
	complete SCI	2
	incomplete SCI	3
	cauda equina syndrome	3
Integrity of posterior ligamantous complex	intact	0
	undetermined	2
	definite injury	3
TLICS = Total Points →		

Table 28-45 Management based on TLICS

TLICS	Management
≤ 3	nonoperative candidates
4	“grey zone” may be considered for operative or nonoperative management
≥ 5	surgical candidates

28.8.2. Surgical treatment

Fragments within the canal: if the PLL is intact (may not be the case with middle column failure), distraction may be able to “pull” the fragments back into their normal position (**ligamentotaxis**) although this is not assured[254]. Ligamentotaxis has a better chance of succeeding if performed within 48 hours of injury. From a posterior approach with laminectomy: intraoperative ultrasound may demonstrate residual canal fragments[255], and if needed the fragments may be impacted anteriorly out of the canal, e.g. using tamps such as Sypert spinal impactors.

CHOICE OF SURGICAL APPROACH

The posterior approach is preferred when there is not a specific need to go from the front.

SPINAL INSTRUMENTATION

Anterior instrumentation of the lower lumbar spine is difficult, and is usually not recommended below ≈ L4.

Burst fractures

There is more than one solution to any given problem, there are a number of controversies, and the following is proposed as a recommendation.

Choice of approach: Surgical considerations: a posterior approach is preferred if there is a dural tear, whereas a burst fracture with partial deficit and canal compromise may be treated more effectively from an anterior approach[243]. A small progression in angular deformity may occur when posterior stabilization is performed alone (since the injury to the anterior column is not corrected), but by itself usually does not require intervention.

For a posterior approach: In ideal situation (good bone quality, pedicle screw placement goes well (i.e. no fracture, no breach), and non-smoking patient) then one can fuse/rod one above and one below the fracture (using pedicle screws; longer constructs are needed with laminar *hooks*). With a short segment fusion like this, approximately 10° of lordosis be lost with time, therefore, one should try to overcorrect a little to accommodate the anticipated settling. If the patient does not meet the above criteria (e.g. poor bone quality), an option is to "rod long, fuse short" (e.g. rod 2 levels above and below the fracture but fuse only 1 level above and below) and then to remove the hardware when the fusion is solid (e.g. at ≈ one year) - this avoids fusing a nonpathologic segment just to get a better anchor. Junctional deterioration to the point that further surgery is needed often occurs at 3 years when 4 segments are fused, whereas it occurs at 8-9 years when only 3 levels are fused. Fusing across critical levels (i.e. thoracolumbar junction with T11 or L1 compression fractures) requires that the fusion incorporate 2-3 levels on each side of the the junction (the forces of the long segment of the relatively immobile thoracic spine with the lumbar spine at the T-L junction increase the risk of nonunion).

Schanz screws work well for applying a lordotic force across the fracture. If

there is bone in the canal, it is important not to overdistract to avoid neural injury. If lordosis is applied withthe rod locking screws loose, the connectors may move closer together which could increase bone within the canal (therefore, either tighten the rod screws or place blocks on the rods before applying lordotic force). If you have gone two above and two below the fracture, first, tighten all retaining nuts (rod and pedicle nuts) on the ends of both rods (8 nuts total). Then place pedicle screw nut tighteners over the pedicle screws in the levels immediately above and below the fracture. Cross the tighteners to reduce the angle of kyphosis, then tighten the nuts. Next distract For distraction, a rod-holder can be placed on the rod to distract against since the gap across the fracture segment (where no pin is placed) may be too long. The rod nuts are then tightened. After a final tightening of all nuts, the pedicle screws are cut off using the insitu cutter.

For thoracic fractures that are not severe and do not require decompression, an option is to place pedicle screws and rods (which can be done percutaneously) without placing any graft. The concept is that the ribs anteriorly and the screws/rods posteriorly provide adequate stabilization while the fractured VB heals. This is more commonly practiced in Europe than the U.S..

Wound infections

Postoperative wound infections with spinal instrumentation are usually due to *Staph. aureus*, and may respond to prolonged antibiotic administration without hardware removal[243]. Persistent infection may respond to debridement of devitalized tissue (e.g. onlay bone graft) and thorough washout without removal of instrumentation followed by antibiotics. If this inadequate, removal of instrumentation may occasionally be required.

28.9. Osteoporotic spine fractures

Osteoporosis is defined as a condition of skeletal fragility as a result of low bone mass, microarchitectural deterioration of bone, or both[256]. It is found most commonly in post-menopausal white females, and is rare prior to menopause. Lifetime risk of symptomatic vertebral body **(VB)** osteoporotic compression fractures is 16% for women, and 5% for men. There are ≈ 700,000 VB compression fractures per year in the U.S.

These patients are often found to have significant VB compression fractures

on plain films after presenting with back pain following a seemingly minor fall. CT often shows an impressive amount of bone retropulsed into the canal.

Risk factors

Factors that increase the risk of osteoporosis include:

1. weight < 58 kg
2. cigarette smoking[257]
3. low-trauma VB fracture in the patient or a first degree relative
4. drugs
    A. heavy alcohol consumption
    B. AEDs (especially phenytoin)
    C. warfarin
    D. steroid use:
        1. bone changes can be seen with 7.5 mg/d of prednisone for > 6 months
        2. VB fractures occur in 30-50% of patients on prolonged glucocorticoids
5. postmenopausal female
6. males undergoing androgen deprivation therapy (e.g. for prostate Ca). Orchiectomy or ≥ 9 doses of gonadotropin-releasing hormone agonists had a 1.5 fold increase in risk of all fractures[258]
7. physical inactivity
8. low calcium intake

Factors that protect against osteoporosis include impact exercise and excess body fat.

DIAGNOSTIC CONSIDERATIONS

To differentiate osteoporotic compression fractures from other pathologic fractures, see *Pathologic fractures of the spine*, page 1232.

Pre-fracture diagnosis

1. measuring bone fragility is not possible
2. the best correlate with bone fragility is radiographic measurement of bone mineral density **(BMD)** using DEXA scan (*see below*)
3. patients with low-trauma fractures or fragility fractures are considered

osteoporotic even if their BMD are greater than these cutoffs

DEXA scan (dual energy x-ray absorptiometry): the preferred way to measure BMD

1. proximal femur: BMD in this location is the best predictor for future fractures
2. LS spine: best location to assess response to treatment (need AP and lateral views, since AP often overestimates BMD because of superimposition of overlying posterior elements and aortic calcifications)
3. forearm BMD may be used if hip or spine are unsuitable

Interpretation of DEXA scan results:

1. findings are reported as
   A. T-score: norms for healthy young adults
   B. Z-score: norms of subjects of same age and sex as the patient
2. diagnostic criteria: WHO definitions[A]

A. with a normal distribution 1 SD below the mean is the lowest 25th percentile, 2 SD below is 2.5th %ile

   A. normal: > –1 standard deviations **(SD)**
   B. osteopenia: from –1 to –2.5 SD
   C. osteoporosis: < than –2.5 SD[259]

Post-fracture considerations

1. other causes of pathologic fracture, especially neoplastic (e.g. multiple myeloma, metastatic breast cancer) should be ruled out
2. younger patients with osteoporosis require evaluation for a remediable cause of the osteoporosis (hyperthyroidism, steroid abuse, hyperparathyroidism, osteomalacia, Cushing’s syndrome)

TREATMENT[260-263]

PREVENTION OF OSTEOPOROSIS

High calcium intake during childhood may increase peak bone mass. Weight-bearing exercise in adulthood helps slow calcium loss from bones. Also

effective: estrogen (*see below*), bisphosphonates (alendronate and risedronate), and raloxifene.

TREATING ESTABLISHED OSTEOPOROSIS

Drugs that increase bone formation include:

1. intermittent low-dose parathyroid hormone: still experimental
2. sodium fluoride: 75 mg/d increases bone mass but did not significantly reduce the fracture rate. 25 mg PO BID of a delayed-release formulation (Slow Fluoride®) reduced fracture rate but may make bone more fragile and could increase risk of hip fractures. Fluoride increases demand for Ca^{++}, therefore supplement with 800 mg/d Ca^{++} and 400 IU/d vitamin D. Not recommended for use > 2 yrs

Drugs that reduce bone resorption are less effective on cancellous bone (found mainly in the spine and at the end of long bones[261]). Medications include:

1. estrogen: cannot be used in men. Studies of estrogen hormone replacement therapy **(HRT)** have shown increased vertebral bone mass by > 5% and decreased rate of vertebral fractures by 50%. Also relieves post-menopausal symptoms and reduces risk of CAD. However, because HRT increases the risk of breast cancer[264] and of breast cancer recurrence[265] as well as DVT, its use has diminished substantially
2. calcium: current recommendations are for 1,000-1,500 mg/d for postmenopausal women[266] taken with meals
3. **vitamin D** or analogues: promote calcium absorption from the GI tract. Typically administered with calcium therapy. Vitamin D 400-800 IU/d is usually sufficient. If urinary Ca^{++} remains low, high dose vitamin D (50,000 IU q 7-10 d) may be tried. Since high-dose formulations have been discontinued in the U.S., analogues such as calcifediol (Calderol®) 50 µg/d or calcitriol (Rocaltrol®) up to 0.25 µg/d may be tried with Ca^{++} supplement. Serum levels of 25-hydroxyvitamin D [25(OH)D], AKA calcidiol is the best indicator of vitamin D status. The significance of vitamin D levels are shown in *Table 28-46*[266]. With high dose vitamin D or analogues, monitor serum and urinary Ca^{++}

Table 28-46 Serum 25-hydroxyvitamin D levels

ng/ml	nmol/L	Interpretation
< 10-11	< 25-27.5	vit D deficiency → rickets (in peds) and osteomalacia (adults)

<10-15	< 25-37.5	inadequate for bone and overall health
≥ 15	≥ 37.5	adequate for bone and overall health
consistently > 200	consistently > 500	potentially toxic → hypercalcemia & hyperphosphatemia

4. calcitonin: derived from a number of sources, salmon is one of the more common. Benefit in preventing fractures is less well established[263]
   A. parenteral salmon calcitonin (Calcimar®, Miacalcin®): indicated for patients for whom estrogen is contraindicated. Expensive ($1,500-3,000/yr) and must be given IM or sub-Q. 30-60% of patients develop antibodies to the drug which negates its effect. ***Rx***: 0.5 ml (100 U) of calcitonin (given with calcium supplements to prevent hyperparathyroidism) SQ q d
   B. intranasal forms (Miacalcin nasal spray): less potent. 200-400 IU/d given in one nostril (alternate nostrils daily) plus Ca^{++} 500 mg/d and vitamin D
5. bisphosphonates: carbon-substituted analogues of pyrophosphate have a high affinity for bone and inhibit bone resorption by destroying osteoclasts. Not metabolized. Remain bound to bone for several weeks
   A. **etidronate** (Didronel®), a 1st generation drug. Not FDA approved for os-*1 ng/ml = 2.5 nmol/L* teoporosis. May reduce rate of VB fractures, not confirmed on F/U. Possible increased risk of hip fractures due to inhibition of bone mineralization may not occur with 2nd & 3rd generation drugs listed below. ***Rx*** 400 mg PO daily **x** 2 wks followed by 11-13 weeks of Ca^{++} supplementation
   B. **alendronate** (Fosamax®): can cause esophageal ulcers. ***Rx*** Prevention: 5 mg PO daily; treatment 10 mg PO daily; taken upright with water on an empty stomach at least 30 minutes before eating or drinking anything else. Once weekly dosing of 35 mg for prevention and 70 mg for treatment[263, 267]. Taken concurrently with 1000-1500 mg/d Ca^{++} and 400/d IU of vitamin D
   C. **risedronate** (Actonel®): ***Rx*** Prevention or treatment: 5 mg PO daily, or 35 mg once/week[267] on an empty stomach (as for alendronate, *see above*)
   D. other drugs not FDA approved for osteoporosis: tiludronate (Skelid®), pamidronate (Aredia®) (some are used for Paget's disease, *see page 501*)
6. estrogen analogues:

A. **tamoxifen** (Nolvadex®), an estrogen antagonist for breast tissue but an estrogen agonist for bone, has a partial agonist effect on uterus associated with an increased incidence of endometrial cancer

B. **raloxifene** (Evista®): similar to tamoxifen but is an estrogen antagonist for uterus[268]. Decreases the effect of warfarin (Coumadin®). ***Rx***: 60 mg PO q d. **Supplied**: 60 mg tablets

7. RANK ligand **(RANKL)** inhibitors: RANKL binds to RANK receptors and stimulates precursor cells to mature into osteoclasts and inhibits their apoptosis[269]. Agents undergoing investigation include denosumab (Prolia®) 60 mg SQ q 6 months appears more effective than alendronate[270]

Treatment of osteoporotic vertebral compression fractures

Patients rarely have neurologic deficit. They are also usually fragile elderly women who usually do not tolerate large surgical procedures well, and the rest of their bones are also osteoporotic which are poor for internal fixation.

Management consists primarily of analgesics and bed rest followed by progressive mobilization, often in an external brace (often not tolerated well). Surgery is rarely employed. In cases where pain control is difficult to obtain or where neural compression causes deficit, limited bony decompression may be considered. Percutaneous vertebroplasty (*see below*) is a newer option.

Typical time course of conservative treatment:

1. initially, severe pain may require hospital or subacute care facility admission for adequate pain control utilizing
   A. sufficient pain medication
   B. bed rest for about 7-10 days (DVT prophylaxis recommended)
2. begin physical therapy **(PT)** after ≈ 7-10 days as patient tolerates (prolonged bed rest can promote “disuse osteoporosis”)
   A. pain control as patient is mobilized may be enhanced by a <u>lumbar brace</u> which may work by reducing movement which causes repetitive “microfractures”
   B. discharge from the hospital with lumbar brace for outpatient PT
3. pain subsides on the average after 4-6 weeks (range 2-12 weeks)

Vertebral body augmentation

Percutaneous vertebroplasty (PVP): Transpedicular injection of polymethylmethacrylate[A] **(PMMA)** “(AKA methylmethacrylate) cement” into

the compressed bone with the following goals:

A. PMMA injection is FDA approved for treatment of compression fractures due to osteoporosis or tumor, but not for trauma (PMMA would prevent healing of the fracture)

1. to *shorten* the duration of pain (sometimes providing pain relief within minutes to hours). Remember: the natural history is that pain will eventually diminish in essentially all of these patients. Mechanism of pain relief may be due to stabilization of bone and/or due to disruption of nerve pain transmission by heat released during the exothermic curing of the cement
2. to try and stabilize the bone: may prevent progression of kyphosis

Recent randomized studies found no benefit in vertebroplasty over a sham procedure at 1 month[271] or at any time up to 6 months post-procedure[272]. NB: kyphoplasty (*see below*) was not studied; use with metastatic spine tumors was also not evaluated. Patient selection issues may make these results more or less generalizable to a specific patient.

Kyphoplasty: Similar to PVP, except first, a balloon is inserted into the compressed VB through the pedicle. The balloon is inflated and then deflated and removed. PMMA is injected into the thusly created defect. Potential benefits of this over vertebroplasty: there may be some restoration of height, and there may be less tendency for PMMA extravasation/embolization (due to the cavity creation and the thicker PMMA used). In the (industry sponsored) randomized non-blinded FREE study[300] there was a significant positive difference in pain reduction and quality of life improvement in the kyphoplasty group compared to the nonoperated group at 1 month that diminished by 1-year post-op.

Indications

1. painful osteoporotic compression fractures:
   A. usually do not treat fractures producing < 5-10% loss of height
   B. severe pain that interferes with patient activity
   C. failure to adequately control pain with oral pain medication
   D. ★ pain localized to fracture level
   E. acute fractures: procedure is not effective for healed fractures. In questionable cases, look for changes on STIR MRI (*see below*)

2. levels: FDA approved for use from T5 through L5, however has been used off-label (primarily for tumor, e.g. multiple myeloma) from T1 through sacrum, and has been described (for tumor) in the cervical spine from an anterior approach
3. vertebral hemangiomas that cause vertebral collapse or neurologic deficit as a result of extension into the spinal canal (not for incidental hemangiomas): *see page 738*
4. osteolytic metastases and multiple myeloma[273]: pain relief and stabilization
5. pathologic compression fractures[274] from metastases: PVP does not give as rapid pain relief as with osteoporotic compression fractures (it may actually be necessary to increase pain meds for 7-10 days post PVP)
6. pedicle screw salvage when pedicle fractures or screws strip during pedicle screw placement

Contraindications

1. coagulopathy
2. completely healed fractures (no edema on MRI or cold on bone scan)
3. active infections: sepsis, osteomyelitis, discitis and epidural abscess
4. spinal instability
5. focal neurologic exam: may indicate herniated disc, retropulsed fragment in canal. Get CT or MRI to rule these out
6. relative contraindications:
   A. fractures > 80% loss of VB height (technically challenging)
   B. acute burst fractures
   C. significant canal compromise from tumor or retropulsed bone
   D. partial or total destruction of the posterior VB wall: not an absolute contraindication
7. iodine allergy: there is a small risk of a balloon rupturing with spill of the iodinated contrast used to fill the balloons prior to injecting the PMMA. Options include: iodine allergy prep (*see page 124*), use of gadolinium instead of iodinated contrast

Complications

Complication = rate: 1-9%. Lowest when used to treat osteoporotic compression fractures, higher with vertebral hemangiomas, highest with

pathological fractures

1. methacrylate leakage:
   A. into soft tissues: usually of little consequence
   B. into spinal canal: symptomatic spinal cord compression is very rare
   C. into neural foramen: may cause radiculopathy
   D. into disc space
   E. venous: can get into spinal venous plexus or vena cava with ≈ 0.3-1% risk of *clinically significant* methacrylate pulmonary embolism (PE)[275]
2. radiculopathy: 5-7% incidence. Some cases may be due to heat released during cement curing. Often treated conservatively: steroids, pain meds, nerve block…
3. pedicle fracture
4. rib fracture
5. transverse process fracture
6. anterior penetration with needle: puncture of great vessels, pneumothorax…
7. increased incidence of future VB compression fractures at adjacent levels

Management of some associated developments

1. chest pain
   A. get rib x-rays
   B. VQ scan if indicated
2. patient starts coughing during injection: fairly common. May be reaction to rib pain or to odor of PMMA, may also indicate solvent in lungs. Stop injecting
3. back pain: take x-ray to rule-out new fracture or PMMA in veins
4. neurologic symptoms: get CT scan

Pre-procedure evaluation

1. plain x-rays: minimum requirement, most practitioners get MRI or bone scan
2. **CT**: helps rule-out <u>bony</u> compromise of spinal canal which may indicate increased risk of leakage for PMMA into canal during procedure
3. **MRI**: not mandatory, may be helpful in some cases
   A. short tau inversion recovery **(STIR)** images demonstrate bone edema indicative of acute fractures (not as good for differentiating

pathology)[276]

   B. MRI can also disclose neurologic compression by <u>soft</u> tissue (e.g. tumor)

4. patients with multiple compression fractures: consider getting **bone scan** and perform PVP in the VB near the level of pain that lights up the most (↑ activity on bone scan correlates strongly with good outcome from PVP)

Booking the case - kyphoplasty

Also see default values (*page v*).

1. position: prone
2. anesthesia: may be done under general, or under MAC
3. equipment: 2 C-arms for biplane fluoro
4. implants:
   A. kyphoplasty set
   B. iodinated contrast from radiology to fill balloons
5. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: insertion of a needle into the fractured/abnormal bone, some-times getting a biopsy as well, and then inflating a balloon in the bone to try and bring it back to a more normal size and then to inject a liquid cement which will then harden inside the bone to strengthen it
   B. alternatives: nonsurgical management, open surgery, in cases of tumor sometimes radiation therapy can be done
   C. complications: leakage of cement which can compress nerves and may need to be removed surgically if possible, rib fracture (from positioning), injury to large blood vessel or lung by the needle, failure to achieve the desired pain relief

Procedure

1. pain medication
   A. remember, this procedure is done with the patient lying on their stomach and is usually performed on frail, elderly females who smoke. Therefore use caution to avoid oversedation and respiratory compromise
   B. sedation and pain medication

C. use of local anesthetic during needle placement
D. additional pain medication just prior to injection

2. use biplane fluoro to pass needle through the pedicle to enter VB (see *Percutaneous pedicle screws*, page 192) and place tip ≈ 1/2 to 2/3 of the way through the VB
3. test inject with contrast (e.g. iohexol (Omnipaque 300) *see page 122*) (do digital subtraction study if equipment is available). For kyphoplasty, the balloon is inflated at this time
   A. a little venous enhancement is acceptable
   B. if you visualize vena cava
      1. do not pull needle back (the fistula has already been created)
      2. push needle in a little further, or
      3. push some gelfoam (soaked in contrast) through the needle, or
      4. inject a very small amount of PMMA under visualization and allow it to set to block the fistula
4. inject PMMA (that has been opacified with tantalum or barium-sulfate) under fluoroscopic visualization until:
   A. 3-5 cc injected (minimal compression fractures accept more cement, some-times up to ≈ 8 cc). No correlation between amount of PMMA injected and pain relief[273]
   B. PMMA approaches posterior VB wall. Stop if cement ever: enters disc space, vena cava, pedicle, or spinal canal

Post-procedure

1. PVP is often an outpatient procedure, but sometimes overnight admission is used
2. watch for
   A. chest or back pain (may indicate rib fracture)
   B. fever: may be reaction to cement
   C. neurologic symptoms
3. activity
   A. gradual mobilization after ≈ 2 hours
   B. ± physical therapy
   C. ± short term use of external brace (most centers do not use)
4. institute medical treatment for osteoporosis: remember the patient with fragility fractures by definition has osteoporosis with risk of future

fractures

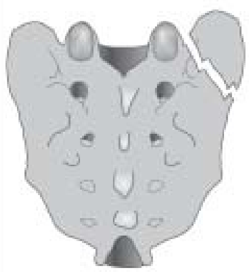
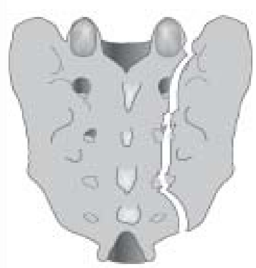
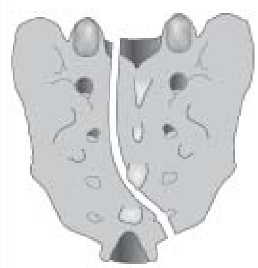
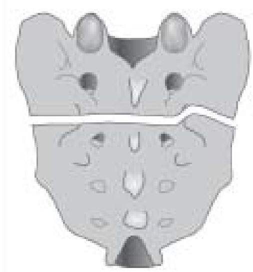
28.10. Sacral fractures

Uncommon. Usually caused by shear forces. Identified in 17% of patients with pelvic fractures[277] (∴ keep in mind that neurologic deficits in patients with pelvic fractures may be due to associated sacral fractures).

The sacrum below S2 is not essential to ambulation or support of the spinal column, but may still be unstable since pressure to the area may occur when supine or sitting.

Neurologic injuries occur in 22-60%[277]. Three characteristic clinical presentations based on zone of involvement[277, 278] as shown in *Table 28-47*.

Table 28-47 Classification of sacral fractures

Zone I	Zone II	Zone III Vertical	Zone III Transverse
			
Zone I: Region of ala sparing the central canal and neural foramina. Occasionally associated with partial L5 root injury possibly as a result of entrapment of the L5 root between the upwardly migrated fracture fragment and the transverse process of the L5 vertebra	**Zone II**: Region of sacral foramina. A vertical fracture which may be associated with unilateral L5, S1 and/or S2 nerve root involvement (producing sciatica). Bladder dysfunction is rare	**Zone III**: Region of sacral canal. Frequently associated with sphincter dysfunction (occurs only with bilateral root injuries) and saddle anesthesia. Subdivided[277]:	
		Vertical: almost always associated with pelvic ring fracture	**Transverse** (horizontal): rare. Often due to a direct blow to the sacrum as in a fall from a great height. Marked displacement of fracture fragment can produce severe deficit* (bowel & bladder incontinence)

* significant deficit is rare in fractures at or below S4

Treatment

In one series[279], all 35 fractures were treated without surgery, and only 1 patient with a complete cauda equina syndrome did not improve. Others feel that

surgery may have a useful role[277]:

1. operative reduction and internal fixation of unstable fractures may aid in pain control and promote early ambulation
2. decompression and/or surgical reduction/fixation may possibly improve radicular or sphincter deficits

Some observations[277]:

1. reduction of the ala may promote L5 recovery with Zone I fractures
2. Zone II fractures with neurologic involvement may recover with or without surgical reduction and fixation
3. horizontal Zone III with severe deficit: controversial. Reduction & decompression does not ensure recovery, which may occur with nonoperative management

28.11. Gunshot wounds to the spine

Most are due to assaults with handguns. Distribution: cervical 19-37%, thoracic 48-64%, and lumbosacral 10-29% (roughly proportional to lengths of each segment). Spinal cord injury due to civilian GSWs are primarily due to direct injury from the bullet (unlike military weapons which may create injury from shock waves and cavitation). Steroids are not indicated (*see page 937*).

Indications for surgery:

1. injury to the cauda equina (whether complete or incomplete) if nerve root compression is demonstrated[280]
2. neurologic deterioration: suggesting possibility of spinal epidural hematoma
3. compression of a nerve root
4. CSF leak
5. spinal instability: very rare with isolated GSW to the spine
6. to remove a copper jacketed bullet: copper can cause intense local reaction[281]
7. incomplete lesions: very controversial. Some series show improvement with surgery[282], others show no difference from unoperated patients
8. debridement to reduce the risk of infection: more important for <u>military</u> GSW where there is massive tissue injury, not an issue for most civilian

GSW except in cases where the bullet has traversed GI or respiratory tract

9. vascular injuries
10. surgery for late complications:
    A. migrating bullet
    B. lead toxicity[283] (plumbism): absorption of lead from a bullet occurs only when it lodges in joints, bursae, or disc space. Findings include: anemia, encephalopathy, motor neuropathy, nephropathy, abdominal colic
    C. late spinal instability: especially after surgery

28.12. Penetrating trauma to the neck

Most often, injuries to the soft-tissues of the neck fall into the purvey of general/trauma surgeons and/or vascular surgeons. However, depending on local practice patterns, neurosurgeons may participate in care of these injuries, or they may get involved by virtue of associated spinal injuries. Also, see *Gunshot wounds to the spine*, page 998.

Trauma surgeons have traditionally divided penetrating injuries of the neck into 3 zones[284], and although definitions vary, the following is a general scheme[285]:

Zone I: inferiorly from the head of the clavicle to include the thoracic outlet
Zone II: from the clavicle to the angle of the mandible
Zone III: from the angle of the mandible to the base of the skull

The mortality rate for penetrating injury to the neck is ≈ 15%, with most early deaths due either to asphyxiation from airway compromise, or exsanguination externally or into the chest or upper airways. Late death is usually due to cerebral ischemia or complications from spinal cord injury.

Vascular injuries: Venous injuries occur in ≈ 18% of penetrating neck wounds, and arterial injuries in ≈ 12%. Of the cervical arteries, the common carotid is most usually involved, followed by the ICA, the ECA, and then the vertebral artery. Outcome probably correlates most closely with neurologic condition on admission, regardless of treatment.

Vertebral artery **(VA)**: the majority of injuries are penetrating. Due to the proximity of other vessels, the spinal cord and nerve roots, injuries are rarely isolated to the VA. 72% of documented VA injuries had no related physical

findings on exam[286].

Evaluation

Neurologic examination: global deficits may be due to shock or hypoxemia due to asphyxiation. Cerebral neurologic deficits are usually due to vascular injury with cerebral ischemia. Local findings may be related to cranial nerve injury. Unilateral UE deficits may be due to nerve root or brachial plexus involvement. Median or ulnar nerve dysfunction can occur from compression by a pseudoaneurysm of the proximal axillary artery. Spinal cord involvement may present with complete injury, or with an incomplete spinal cord injury syndrome (*see page 948*). Shock due to spinal cord injury is usually accompanied by bradycardia (*see page 930*), as opposed to the tachycardia seen with hypovolemic shock.

Cervical spine x-rays: assesses trajectory of injury and integrity C-spine.

Angiography: indicated in most cases if the patient is stable (especially for zone I or III injuries, and for zone II patients with no other indication for exploration, or for patients with penetration of the posterior triangle or wounds near the transverse processes where the VA may be injured). Patients actively hemorrhaging need to be taken to the OR without pre-op angiography. Angiographic abnormalities include:

1. extravasation of blood
   A. expanding hematoma into soft tissues: may compromise airway
   B. pseudoaneurysm
   C. AV fistula
   D. bleeding into airways
   E. external bleeding
2. intimal dissection, with
   A. occlusion, or
   B. luminal narrowing (including possible “string sign”)
3. occlusion by soft tissue or bone

Treatment

Airway: stable patients without airway compromise should not have “prophylactic” intubation to protect the airway. Immediate intubation is indicated for hemodynamically unstable patients or for airway compromise. Options:

1. endotracheal: preferred

2. cricothyroidotomy: if endotracheal intubation cannot be performed (e.g. due to tracheal deviation or patient agitation) or if there is evidence of cervical spine injury and manipulation of the neck is contraindicated, then cricothyroidotomy is performed with placement of a #6 or 7 cuffed endotracheal tube (followed by a standard tracheostomy in the OR once the patient is stabilized)
3. awake nasotracheal: may be considered in the setting of possible spinal injury

Exploration: surgical exploration has been advocated for all wounds that pierce the platysma and enter the anterior triangles of the neck[287], however, 40-60% of these explorations will be negative. Although a selective approach may be based on angiography, false negatives have resulted in some authors recommending exploration of all zone II injuries[288].

Carotid artery: choices are primary repair, interposition grafting, or ligation. Patients in coma or those with severe strokes caused by vascular occlusion of the carotid artery are poor surgical candidates for vascular reconstruction due to a high mortality rate ≥ 40%[285], however the outcome with ligation is worse. Repair of injuries is recommended in patients with no or only minor neurologic deficit. ICA ligation is recommended for bleeding that cannot be controlled and was used for extravasation of dye at the base of the skull in 1 patient[289].

Vertebral artery: injuries are more often managed by ligation than by direct repair[290], especially when bleeding occurs during exploration. Less urgent conditions (e.g. AV fistula) requires knowledge of the patency of the contralateral VA and the ability to fill the ipsilateral PICA from retrograde flow through the BA before ligation can considered (arteriographic anomalies contraindicate ligation in 15% of cases). Proximal occlusion may be accomplished with an anterior approach after the sternocleidomastoid is detached from the sternum. The VA is the normally the first branch of the subclavian artery. Alternatively, endovascular techniques may be used, e.g. detachable balloons for proximal occlusion, or thrombogenic coils for pseudoaneurysms. Distal interruption may also be required, and this necessitates surgical exposure and ligation. Optimal management of a thrombosed injured VA in a foramen transversarium is unknown, and may require arterial bypass if ligation is not a viable option.

28.13. Delayed deterioration following spinal cord injuries

Etiologies include:

1. posttraumatic syringomyelia: *see page 513*. Latency to symptoms: 3 mos-34 yrs
2. subacute progressive ascending myelopathy **(SPAM)**: rare. Median time of occurrence: 13 days post injury (range: 4-86 days)[291]. Signal changes extending to ≥ 4 levels above the original injury
3. unrecognized spinal instability[292]: mean delay in diagnosis was 20 days
4. tethered spinal cord: may be due to scar tissue at site of injury
5. delayed spinal epidural hematoma (SEH): most symptomatic SEH occur within 72 hours of surgery, however longer delays have been reported[293]
6. apoptosis of neurons, oligodendrogliocytes, and astrocytes[294]: initiated during the acute phase, deterioration occurs during the chronic phase of SCI (months to years after SCI)
7. glial scar formation: mass effect as well as release of factors that may damage surviving neurons[295 (p 43-5)]

28.14. Chronic management issues with spinal cord injuries

Most of the following topics are treated elsewhere in this manual, but are pertinent to spinal cord injured **(SCI)** patients, and reference to the specific section is made.

1. autonomic hyperreflexia: *see below*
2. **ectopic bone**, includes **para-articular heterotopic ossification**: ossification of some joints that occurs in 15-20% of paralyzed patients
3. osteoporosis and pathologic fracture: *see page 992*
4. spasticity: *see page 536*
5. syringomyelia: *see page 510*
6. deep vein thrombosis: *see below* and also *page 42*
7. shoulder-hand syndrome: possibly sympathetically maintained

RESPIRATORY MANAGEMENT PROBLEMS IN SPINAL CORD INJURIES

In attempting to wean high level SCI patients from a ventilator, it may be helpful to change tube feedings to Pulmonaid® which lowers the CO_2 load.

Patients with cervical SCIs are more prone to pneumonia due to the fact that most of the effort in a normal cough originates in the abdominal muscles which are paralyzed.

AUTONOMIC HYPERREFLEXIA

Key concepts:

> - exaggerated autonomic response to normally innocuous stimuli
> - in spinal cord injury, occurs only in patients with lesions <u>above</u> ≈ T6
> - patients complain of pounding headache, flushing and diaphoresis above lesion
> - can be life threatening, requires rapid control of hypertension and a search for an elimination of offending stimuli

AKA autonomic dysreflexia. Autonomic hyperreflexia[296, 297] **(AH)** is an exaggerated autonomic response (sympathetic usually dominates) secondary to stimuli that would only be mildly noxious under normal circumstances. It occurs in ≈ 30% of quadriplegic and high paraplegic patients (reported range is as high as 66-85%), but does not occur in patients with lesions below T6 (only patients with lesions above the origin of the splanchnic outflow are prone to develop AH, and the origin is usually T6 or below). It is rare in first 12-16 weeks post-injury.

During attacks, norepinephrine **(NE)** (but not epinephrine) is released. Hypersensitivity to NE may be partially due to subnormal resting levels of catecholamines. Homeostatic responses include vasodilatation (above the level of the injury) and bradycardia (however, sympathetic stimulation may also cause tachycardia).

Stimulus sources causing episodes of autonomic hyperreflexia:

1. bladder: 76% (distension 73%, UTI 3%, bladder stones…)
2. colorectal: 19% (fecal impaction 12%, administering enema or suppository 4%)
3. decubitus ulcers/skin infection: 4%
4. DVT
5. miscellaneous: tight clothing or leg bag straps, procedures such as

cystoscopy or debriding decubitus ulcers, case report of suprapubic tube

Presentation

- paroxysmal HTN: 90%
- anxiety
- diaphoresis
- piloerection
- pounding H/A
- ocular findings:
  - mydriasis
  - blurring of vision
  - lid retraction or lid lag
- erythema of face, neck and trunk: 25%
- pallor of skin below the lesion (due to vasoconstriction)
- pulse rate: tachycardia (38%) or mild elevation over baseline, bradycardia (10%)
- "splotches" over face and neck: 3%
- muscle fasciculations
- increased spasticity
- penile erection
- Horner's syndrome
- triad seen in 85%: cephalgia (H/A), hyperhidrosis, cutaneous vasodilatation

Evaluation

In the appropriate setting (e.g. a quadriplegic patient with an acutely distended bladder), the symptoms are fairly diagnostic.

Many features are also common to pheochromocytoma. Studies of catecholamine levels have been inconsistent, however they can be mildly elevated in AH. The distinguishing feature of AH is the presence of hyperhidrosis and flushing of the face in the presence of pallor and vasoconstriction elsewhere on the body (which would be unusual for a pheochromocytoma).

Treatment

1. immediately elevate HOB (to decrease ICP), check BP q 5 min
2. treatment of choice: identify and eliminate the offending stimulus

A. make sure bladder is empty (if catheterized check for kinks or sediment plugs). Caution: irrigating bladder may exacerbate AH (consider suprapubic aspiration)
B. check bowels (avoid rectal exam, may exacerbate). Palpate abdomen or check abdominal x-ray (AH from this usually resolves spontaneously without manual disimpaction)
C. check skin and toenails for ulceration or infection
D. remove tight apparel

3. HTN that is extreme or that does not respond quickly may require treatment to prevent seizures and/or cerebral hemorrhage/hypertensive encephalopathy. Caution must be used to prevent hypotension following the episode. Agents used include: sublingual nifedipine[298] 10 mg SL, IV phentolamine (alpha cholinergic blocker, *see page 681*) or nitroprusside (Nipride®) (*see page 19*)
4. consider diazepam (Valium®) 2-5 mg IVP (@ < 5 mg/min). Relieves spasm of skeletal and smooth muscle (including bladder sphincter). Is also anxiolytic

PREVENTION

Good bowel/bladder and skin care are the best preventative measures.

Prophylaxis in patients with recurrent episodes

1. phenoxybenzamine (Dibenzyline®): an alpha blocker. Not helpful during the acute crisis. May not be as effective for alpha stimulation from sympathetic ganglia as with circulating catecholamines[299]. The patient may also develop hypotension after the sympathetic outflow subsides. Thus this is used only for resistant cases (note: will not affect sweating which is mediated by acetylcholine).

   ***Rx* Adult**: wide range quoted in literature: average 20-30 mg PO BID
2. beta-blockers: may be necessary in addition to α-blockers to avoid possible hypotension from $ß_2$ receptor stimulation (a theoretical concern)
3. phenazopyridine (Pyridium®): a topical anesthetic that is excreted in the urine. May decrease bladder wall irritation, however, the primary cause of irritation should be treated if possible.

   ***Rx* Adult**: 200 mg PO TID after meals. **SUPPLIED**: 100, 200 mg tabs.
4. "radical measures" such as sympathectomy, pelvic or pudendal nerve section, cordectomy, or intrathecal alcohol injection have been advocated

in the past, but are rarely necessary and may jeopardize reflex voiding

5. prophylactic treatment prior to procedures may employ use of anesthetics even in regions rendered anesthetic by the cord injury. Nifedipine 10 mg SL has also been used effective for AH during cystoscopy and prophylactically[298]

28.15. References

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NOTES

29. Stroke

AKA cerebral infarction. The term stroke is preferred to cerebrovascular accident **(CVA)**, although "CVA" is used widely (sometimes as an abbreviation for stroke).

Also see *Occlusive cerebro-vascular disease*, page 1144, *Intracerebral hemorrhage* on page 1118, and *SAH and aneurysms* on page 1034 for those related topics.

DEFINITIONS

TIA	(transient ischemic attack): transient neuronal dysfunction secondary to focal ischemia (of brain, spinal cord, or retina) without (permanent) acute infarction[1]* 10-15% of patients with TIA have a stroke within 3 months, 50% of which occur within 48 hours.
stroke	AKA cerebrovascular accident (sometimes called completed stroke). A permanent (i.e. irreversible) neurologic deficit caused by inadequate perfusion of a region of brain or brain stem

* obsolete operational definitions used an arbitrary 24 hour cutoff for duration of symptoms

29.1. Cerebrovascular hemodynamics

CEREBRAL BLOOD FLOW (CBF) AND OXYGEN UTILIZATION

Table 29-1 shows typical CBF values and the corresponding neurophysiologic state. CBF < 20 is generally associated with ischemia and if prolonged will produce cell death[2]. However, this assumes normal metabolic rate and may be more applicable to *global* cerebral hypoperfusion[3]. There is a higher CBF threshold for loss of electrical excitability than that for cell death - this has lead to the concept of the ischemic **penumbra** - non-functioning cells that are still viable[2].

CBF is related to blood pressure as shown in *Eq 29-1*,

$$CBF = \frac{CPP}{CVR} = \frac{MAP - ICP}{CVR}$$ Eq 29-1

where CPP = cerebral perfusion pressure (*see page 866*), CVR = cerebrovascular resistance (*see below*), and MAP = mean arterial pressure.

Cerebrovascular resistance (CVR) is affected by the $PaCO_2$ such that there is a linear increase in CBF with increasing $PaCO_2$ within the range of 20-80 mm Hg.

CVR is also affected by changes in CPP which produce changes in blood vessel tone via a myogenic mechanism. In the range of CPP = 50-150 mm Hg the CVR of normal brain tissue varies linearly to maintain an almost constant CBF. This phenomenon is called (cerebral) **autoregulation**, which is altered in pathologic states.

The **cerebral metabolic rate of oxygen consumption ($CMRO_2$)** averages 3.0-3.8 ml/100 gm tissue/min. The ratio of CBF to $CMRO_2$ (the **coupling** ratio[4]) in the quiescent brain is 14-18. With focal cortical activity, local CBF increases ≈ 30% while $CMRO_2$ increases ≈ 5%[5]. $CMRO_2$ can be manipulated to some degree (*see page 1063*).

Table 29-1 Correlates of CBF

CBF (ml per 100 gm tissue/min)		Condition
> 60 (approx)		hyperemia (CBF > tissue demand)
45-60		normal brain at rest
75-80		gray matter
20-30		white matter
ISCHEMIA	16-18	EEG becomes flatline
	15	physiologic paralysis
	12	brainstem auditory evoked response (BAER) changes
	10	alterations in cell membrane transport (cell death; stroke)

CEREBROVASCULAR RESERVE & REACTIVITY

May be evaluated with xenon-enhanced CT, CTP (*see page 128*), TCD, SPECT, or MRI[98-101]. Response of CBF to a vasodilator challenge with 1000 mg of IV acetazolamide **(ACZ)** (Diamox®) is classified as[100, 101]:

Type I: normal baseline CBF with 30-60% increase following ACZ

challenge

Type II: decreased baseline CBF with blunted response of < 10% increase or < 10 mL/100 g/min absolute increase after ACZ challenge

Type III: decreased baseline CBF with paradoxical decrease of regional CBF following ACZ challenge, suggesting a steal phenomenon in regions with maximally dilated vasculature at baseline

29.2. Strokes: general information

ABRUPT ONSET OF NEW FOCAL DEFICIT

For a patient presenting to the E/R with the abrupt onset of a new focal cerebral deficit:

- 5% are seizure, tumor, or psychogenic
- 95% are vascular (i.e stroke):
  - 85% ischemic infarct: early angiography has shown that arterial occlusion can be demonstrated in 80% of these, regardless of subtype[6]
    - 41% unknown cause (may decrease with the use of early angiography)
    - 21% lacune (small artery or arteriole cerebrovascular lesion)
    - 16% cardiogenic embolus[7]
    - 11% large artery cerebrovascular lesion
    - 11% tandem arterial pathology
    - atherosclerotic plaques in the aortic arch > 4 mm thick are a risk factor for recurrent strokes and other vascular events (MI, peripheral embolism, and death from vascular causes)[8]
  - 15-30% hemorrhagic[A]:
    - intracerebral hemorrhage (ICH): ≈11%. "Hypertensive" hemorrhage, amyloid angiopathy (*see page 1122*)…
    - SAH: ≈ 7%. Aneurysmal, AVM-related
    - SDH
  - venous infarction: a small proportion of strokes. Typically seen in dural sinus thrombosis (*see page 1166*)

A. intracerebral hemorrhage **(ICH)** should be suspected with smooth onset of symptoms over minutes to hours, presence of severe H/A, frequent vomiting, and when depression of level of consciousness is

prominent (in contrast to ischemic infarct which typically has significant motor or sensory deficit with little or no impairment of consciousness except with massive or brainstem stroke); these features may be less prominent in lobar ICH. Also see *Intracerebral hemorrhage*, page 1118

29.2.1. Modifiable risk factors for stroke

1. **hypertension**: the most powerful & treatable risk factor. Both systolic & diastolic BP independently correlate with risk of stroke[9]
2. **cigarette smoking**: relative risk values of 1.5-2.210-12
3. **blood lipids**: lowering lipids may reduce the risk of some types of cerebrovascular disease. Current recommendations: treat if LDL > 70. Use of a statin drug is recommended
4. **alcohol**: heavy consumption is associated with increased risk of stroke, whereas moderate use may have no effect or may be slightly protective. The effects may be different for ischemic vs. hemorrhagic stroke[13]
5. **antiplatelet therapy**: reduces the risk of stroke and other vascular events in high-risk patients. The optimal dose is not known, the acceptable range for aspirin is 30-1300 mg/d, with a recommended initial dose of 325 mg/d[14]

29.2.2. Rationale for acute stroke treatment

In the complete absence of blood flow, neuronal death occurs within 2-3 minutes from exhaustion of energy stores. However, in most strokes, there is a salvageable penumbra (tissue at risk) that retains viability for a period of time through suboptimal perfusion from collaterals. Progression of local cerebral edema from the injury results in compromise of these collaterals and progression of ischemic penumbra to infarction if flow is not restored and maintained. Prevention of this secondary neuronal injury drives the treatment of stroke and has led to the creation of designated Primary Stroke Centers that offer appropriate and timely triage and treatment of all potential stroke patients.

Current standard of care requires the administration of IV tPA to all eligible patients. Documentation is necessary to justify deviation from this standard of care in the current medicolegal environment.

In centers with advanced capabilities (Comprehensive Stroke Centers), other treatment modalities are also offered.

29.2.3. Evaluation

HISTORY - KEY COMPONENTS

- time last seen normal (stroke on awakening being increasingly evaluated by perfusion studies to ensure the presence of viable tissue)
- current deficit and clinical presentation
- NIH Stroke Scale score should be assessed and recorded (*see page 1014*)
- reasons for not administering IV tPA (if any) should be documented

CAT SCAN (EMERGENT)

Upon presentation with symptoms of a potential stroke, a noncontrast brain CT scan should be done immediately to rule-out hemorrhage (intraparenchymal or SAH), hematoma, early signs of ischemia, old infarcts or injuries, and other lesions (e.g. tumor).

CAT scan findings with ischemic stroke ("pale" infarcts)

NB: These principles do not apply to small lacunar infarcts, nor to hemorrhagic strokes.

NB: CT is normal in 8-69% of MCA strokes in the first 24 hours[15].

Hyperacute (< 6 hours after stroke): Early signs of infarction involving large areas of the MCA territory correlate with poor outcome[16]. Early findings may include[17]:

1. hyperdense artery sign (*see below*): low sensitivity, but helpful if present
2. focal low attenuation within the gray matter[A]
3. loss of the gray-white interface[A]
4. attenuation of the lentiform nucleus
5. mass effect[A]
   - A. early: effacement of the cerebral sulci (often subtle)[19]
   - B. late: midline shift in large territory infarction
6. loss of the insular ribbon (hypodensity involving the insular region)
7. enhancement: occurs in only 33%. Stroke becomes isodense (called "masking" effect) or hyperdense with normal brain, and, rarely, may be the only indication of infarction[19]

A. these findings are probably due to increased water content resulting from the following: cellular edema arising from altered cell permeability which produces a shift of sodium and water from the extra-cellular to the intracellular compartment, which also increases the extracellular osmotic pressure causing transudation of water from capillaries into the interstitium[18]

24 hrs: Most strokes can be identified as a low density by this time.

1-2 wks: Strokes are sharply demarcated.

3 wks: Stroke approaches CSF density.

In 5-10% there may be a short window (at around day 7-10) where the stroke becomes isodense, called "fogging effect". IV contrast will usually demonstrate these.

Mass effect: common between day 1 to 25. Then atrophy is usually seen by ≈ 5 wks (2 wks at the earliest). Serial CT scans have shown that midline shift increases after ischemic stroke and reaches a maximum 2-4 days after the insult.

Calcifications: only ≈ 1-2% of strokes calcify (in adults, it is probably a much smaller fraction than this; and in peds it is a higher percentage than this). Therefore, in an adult, calcifications almost rule-out a stroke (consider AVM, low grade tumor…).

Hyperdense artery sign: The cerebral vessel (usually the MCA) appears as a high density on unenhanced CT, indicating intraarterial clot (thrombus or embolus)[20]. Seen in 12% of 50 patients scanned within 24 hrs of stroke, and in 34% of 23 very early CTs done to R/O hemorrhage. Sensitivity for MCA occlusion is low, but specificity is high (although it may also be seen with carotid dissection, or (usually bilaterally) with calcific atherosclerosis or high hematocrit[20]). Does not have independent prognostic significance[21].

Enhancement: CT enhancement with IV contrast in stroke:

1. many enhance by day 6, most by day 10, some will enhance up to 5 wks
2. **rule of 2's**: 2% enhance at 2 days, 2% enhance at 2 mos
3. **gyral enhancement**: AKA called "ribbon" enhancement. Common. Usually seen by 1 week (grey matter enhances > white). DDx includes inflammatory infiltrating lesions such as lymphoma, neurosarcoidosis… (due to breakdown of BBB)
4. rule of thumb: there should not be enhancement at the same time there is

mass effect

CT ANGIO ***(CTA)***

CTA (*see page 128*) is useful for assessing the location and extent of vascular occlusion in acute ischemic stroke[22], and may identify the bleeding source in subarachnoid hemorrhage. Findings can direct treatment towards endovascular options when a proximal or significant large vessel occlusion is seen (*see page 1018*).

CT PERFUSION

Theoretically identifies salvageable penumbra as a region of mismatch between CBF and CBV. Assumption: the infarcted core (with no salvageable tissue) has decreased CBF within a region of decreased CBV (CBF/CBV match). A mismatched area (decreased CBV without a decrease in CBF) represents potentially salvageable penumbra[23]. Implication: thrombolytics and interventional treatment modalities without mismatch will likely increase morbidity and mortality without clinical benefit.

MRI

With newer, faster acquisition times, and with gradient echo sequences that are highly sensitive to hemorrhage, MRI is increasingly being utilized in the hyperacute setting and is at times replacing CT as the initial evaluation. More sensitive than CT (especially DWI-MRI (*see page 132*) - and particularly in the 1st 24 hrs after stroke), and especially with brainstem or cerebellar infarction. More contraindications than CT (*see page 130*).

Contrast MRI: not often used. 4 enhancement patterns[24]:

1. intravascular enhancement: occurs in ≈ 75% of 1-3 day-old cortical infarcts, and is probably due to sluggish flow and vasodilatation (thus, it is not seen with complete occlusion). May indicate areas of brain at risk of infarction
2. meningeal enhancement: especially involving the dura. Seen in 35% of cortical strokes 1-3 days old (not seen in deep cerebral or brainstem strokes). No angiographic nor CT equivalent
3. transitional enhancement: above two types of enhancement coexist with early evidence of BBB breakdown; usually seen on days 3-6
4. parenchymal enhancement: classically appears as a cortical or subcortical gyral ribbon enhancement. May not be apparent for the first 1-2 days, and

gradually approaches 100% by 1 week. Enhancement may eliminate "fogging effect" (as on CT) which may obscure some strokes at ≈ 2 weeks on unenhanced T2WI

MRI PERFUSION

Similar to CT perfusion (*see page 132*), areas of matched DWI and PWI abnormality are thought to represent infarcted tissue. PWI abnormalities that do not have a DWI correlate are thought to represent potentially salvageable penumbra[25].

EMERGENCY CEREBRAL ANGIOGRAPHY

Indications:

1. early stroke in carotid distribution + history of amaurosis fugax or bruit or retinal emboli, etc. suggesting increasing carotid stenosis, thrombogenic ulcerated plaque, or carotid dissection
2. if diagnosis still questionable (e.g. aneurysm, vasculitis)
3. with rapid recovery, suggesting carotid TIA in face of increasing stenosis
4. AVOID angio if unstable or if severe disabling neuro deficit

Findings:

1. cutoff sign: vessel ends abruptly at the point of obstruction
2. string sign: narrow strand of contrast in a vessel with high grade stenosis
3. "**luxury perfusion**": reactive hyperemia is a recognized response of cerebral tissue to injury (trauma, infarction, epileptogenic focus…). Luxury perfusion is blood flow in excess of demand due to abolition of CBF autoregulation due to acidosis[26]. On angiography it shows up as accelerated circulation adjacent to the infarct with a stain or blush and early venous drainage

NIH STROKE SCALE (NIHSS)[A]

Administer in order shown. Record initial performance only (do not go back).

Higher NIHSS scores correlate with more proximal vascular lesions (larger vessel occlusion causes more widespread deficit).

A Revised 1/24/91. Based on Cincinnati stroke scale[27]. Contact the Public Health Service, National Institutes of Health, National Institute of Neurologic Disorders and Stroke, Bethesda, Maryland, U.S.A.

for copies of a grading form (which has more details on some aspects of grading) and for training information[28]

1a. Level of consciousness (LOC)

0 alert; keenly responsive

1 not alert, but arousable by minor stimulation to obey, answer or respond

2 not alert, requires repeated stimulation to attend, or is obtunded and requires strong painful stimulation to make movements (not stereotyped)

3 comatose: responds only with reflex motor (posturing) or autonomic effects, or totally unresponsive, flaccid and areflexic

1b. Level of consciousness questions

Patient is asked the month and their age.

0 answers both questions correctly: must be correct (no credit for being close)

1 answers one question correctly, or cannot answer because of: ET tube, orotracheal trauma, severe dysarthria, language barrier, or any other problem not secondary to aphasia.

2 answers neither question correctly, or is: aphasic, stuporous, or does not comprehend the questions

1c. Level of consciousness commands

Patient is asked to open and close the eyes, and then to grip and release the non-paretic hand. Substitute another 1-step command if both hands cannot be used. Credit is given for an unequivocal attempt even if it cannot be completed due to weakness. If there is no response to commands, demonstrate (pantomime) the task. Record only first attempt.

0 performs both tasks correctly

1 performs one task correctly

2 performs neither task correctly

2. Best gaze

Test only horizontal eye movement. Use motion to attract attention of aphasic patients.

0 normal

1 partial gaze palsy (gaze abnormal in one or both eyes, but forced deviation or total gaze paresis are not present) or patient has an isolated cranial nerve III, IV or VI paresis

2 forced deviation or total gaze paresis not overcome by oculocephalic (Doll's eyes) maneuver (do not do caloric testing)

3. Visual

Visual fields (upper and lower quadrants) are tested by confrontation. May be scored as normal if patient looks at side of finger movement. Use ocular threat where consciousness or comprehension limits testing. Then test with double sided simultaneous stimulation **(DSSS)**.

0 no visual loss

1 partial hemianopia (clear cut asymmetry), or extinction to DSSS

2 complete hemianopia

3 bilateral hemianopia (blind, including cortical blindness)

4. Facial palsy

Ask patient (or pantomime) to show their teeth, or raise eyebrows and close eyes. Use painful stimulus and grade grimace response in poorly responsive or non-comprehending patients.

0 normal symmetrical movement

1 minor paralysis (flattened nasolabial fold, asymmetry on smiling)

2 partial paralysis (total or near total paralysis of lower face)

3 complete paralysis of one or both sides (absent facial movement in upper and lower face)

5. Motor Arm (5a = left, 5b = right)

Instruct patient to hold the arms outstretched, palms down (at 90° if sitting, or 45° if supine). If consciousness or comprehension impaired, cue patient by actively lifting arms into position while verbally instructing patient to maintain position.

0 no drift (holds arm at 90° or 45° for full 10 seconds)

1 drift (holds limbs at 90° or 45° position, but drifts before full 10 seconds but does not hit bed or other support)

2 some effort against gravity (cannot get to or hold initial position, drifts

down to bed)

3 no effort against gravity, limb falls

4 no movement 9 amputation or joint fusion: explain

6. Motor leg (6a = left, 6b = right)

While supine, instruct patient to maintain the non-paretic leg at 30°. If consciousness or comprehension impaired, cue patient by actively lifting leg into position while verbally instructing patient to maintain position. Then repeat in paretic leg.

0 no drift (holds leg at 30° full 5 seconds)

1 drift (leg falls before 5 seconds, but does not hit bed)

2 some effort against gravity (leg falls to bed by 5 seconds)

3 no effort against gravity (leg falls to bed immediately)

4 no movement 9 amputation or joint fusion: explain

7. Limb ataxia

(Looking for unilateral cerebellar lesion). Finger-nose-finger and heel-knee-shin tests are performed on both sides. Ataxia is scored only if clearly out of proportion to weakness. Ataxia is absent in the patient who cannot comprehend or is paralyzed.

0 absent

1 present in one limb

2 present in two limbs

9 amputation or joint fusion: explain

8. Sensory

Test with pin. When consciousness or comprehension impaired, score sensation normal unless deficit clearly recognized (e.g. clear-cut asymmetry of grimace or withdrawal). Only hemisensory losses attributed to stroke are counted as abnormal.

0 normal, no sensory loss

1 mild to moderate sensory loss (pin-prick dull or less sharp on the affected side, or loss of superficial pain to pinprick but patient aware of being touched)

2 severe to total (patient unaware of being touched in the face, arm and leg)

9. Best language

In addition to judging comprehension of commands in the preceding neurologic exam, the patient is asked to describe a standard picture, to name common items, and to read and interpret the standard text in the box below. The intubated patient should be asked to write.

You know how.
Down to earth.
I got home from work.
Near the table in the dining room.
They heard him speak on the radio last night.

0 normal, no aphasia
1 mild to moderate aphasia (some loss of fluency, word finding errors, naming errors, paraphasias and/or impairment of communication by either comprehension or expression disability)
2 severe aphasia (great need for inference, questioning and guessing by listener; limited range of information can be exchanged)
3 mute or global aphasia (no usable speech or auditory comprehension) or patient in coma (item 1a = 3)

10. Dysarthria

Patient may be graded based on information already gleaned during evaluation. If patient is thought to be normal, have them read (or repeat) the standard text shown in this box.

MAMA
TIP-TOP

FIFTY-FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

CATERPILLAR

0 normal speech

1 mild to moderate (slurs some words, can be understood with some difficulty)

2 severe (unintelligible slurred speech in the absence of, or out of proportion to any dysphasia, or is mute/anarthric)

9 intubated or other physical barrier

11. Extinction and inattention (formerly neglect)

Sufficient information to identify neglect may already be gleaned during evaluation. If the patient has severe visual loss preventing visual DSSS, and the cutaneous stimuli are normal, the score is normal. Scored as abnormal only if present.

0 normal, no sensory loss

1 visual, tactile, auditory, spatial or personal inattention or extinction to DSSS in one of the sensory modalities

2 profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.

A. Distal motor function (not part of NIHSS) (a = left arm, b = right)

Patients hand is held up at the forearm by the examiner, and is asked to extend the fingers as much as possible. If patient cannot do so, the examiner does it for them. Do not repeat the command.

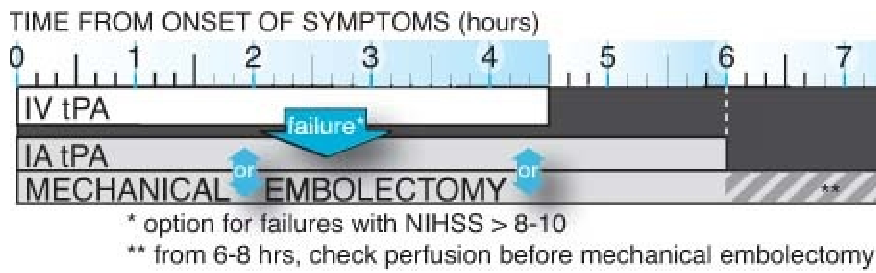
0 normal (no finger flexion after 5 seconds)

1 at least some extension after 5 seconds (any finger movement is scored)

2 no voluntary extension after 5 seconds

29.2.4. Management of TIA or stroke

Treatment options timeline



Σ

1. within 4.5 hours of onset of symptoms:
   - A. patients may be candidates for IV tPA (*see* *page 1017*)
   - B. failures to respond to IV tPA who are in good clinical grade (NIHSS > 8-10, *see* *page 1014*) may be candidates for
     1. intraarterial tPA (IA tPA) or
     2. mechanical embolectomy/clot disruption
2. 4.5-6 hours after onset:
   - A. intraarterial tPA (IA tPA) or
   - B. mechanical embolectomy/clot disruption
3. 6-8 hours, check perfusion with CTP or MRI-DWI before mechanical embolectomy (studied up to 8 hours after onset). ✖ Embolectomy contraindicated if stroke > 1/3 of MCA distribution (risk of ICH with reperfusion)

These times are more applicable to anterior circulation strokes. Posterior circulation occlusions may be treated more aggressively, e.g. IA tPA has been used up to 12 hrs.

THROMBOLYTIC THERAPY

Plasminogen activators catalyze the conversion of plasminogen to the fibrinolytic compound plasmin. The primary agent used is alteplase (recombinant tissue plasminogen activator **(rtPA**, or just **tPA)**) (Activase®) which is FDA approved for the IV treatment of acute ischemic stroke (*see below*).

TISSUE PLASMINOGEN ACTIVATOR

IV tPA

A randomized double-blind NINDS study of 624 patients with an ischemic stroke having a clearly defined time of onset and a CT scan prior to drug administration, found improved neurologic outcome at 3 months in patients who received alteplase (these patients were 30% more likely to have minimal or no disability)[29] which persisted at 6 and 12 mos[30] in all subgroups of *ischemic* stroke. The recurrent stroke rate in control and tPA patients was similar (5%). In contrast, statistical benefit at 90 days could not be confirmed in the second European Cooperative Acute Stroke Study (ECASS II)[31].

Early data indicated tPA had to be given ≤ 3 hrs after the onset of symptoms, however, this window was extended to **4.5 hours** after the ECASS-III[32] looked at 821 stroke patients randomized between placebo or tPA in the 3- to 4.5-hour time-window. Compared to placebo, tPA-treated patients experienced a 7.2% absolute increase in the rate of excellent recovery at 90-day follow-up (P=0.04). Although tPA therapy was associated with an increased rate of symptomatic intracerebral hemorrhage (7.9% for tPA versus 3.5% for placebo, P<0.001), it was not associated with an increased rate of death (7.7% for tPA versus 8.4% for placebo, P=0.68). For every 100 acute ischemic stroke patients given tPA in accordance with the NINDS protocols, 32 will benefit and 3 will be harmed[33].

Guidelines for the administration of IV tPA

Also see http://www.stroke-site.org (The Brain Attack Coalition - NINDS).

h**Eligibility:**

1. age ≥ 18 years (although use in childhood stroke is increasing[34])
2. time last seen normal < 3 hrs prior (ECASS III extends window to 4.5 hours in select[A] patients[35])
3. "wake-up" stroke (seen in 25% of ischemic stroke patients) may also be safe to treat in select circumstances[36]

A. ECASS III did not include: patients ≥ 80 years of age, patients with baseline NIHSS scores > 25 (*see page 1014*), and prior stroke in diabetics. These patients are not excluded from treatment with IV tPA in the 0-3-hour window by the regulatory authorities in the United States and Canada.

Contraindications: (see http://www.stroke-site.org and reference[29])

1. intracerebral hemorrhage **(ICH)**: on admitting CT, or history of prior ICH

2. clinical presentation of SAH (even with negative CT)
3. known intracranial aneurysm or AVM
4. active internal bleeding
5. known bleeding diathesis, including but not limited to:
   A. patients on anticoagulants, or those who received heparin in past 48 hrs
   B. platelet count < 100,000/mm^3
6. serious head trauma, serious stroke, or intracranial surgery within past 3 months
7. SBP > 185 mm Hg, or DBP > 110 mm Hg that cannot be controlled despite use of nicardipine infusion or IV labetalol

Cautions:

1. seizure witnessed at the time of onset of stroke symptoms
2. major surgery within the last 14 days
3. arterial puncture at non-compressible site within past 7 days
4. recent lumbar puncture
5. rapidly improving or minor symptoms
6. blood glucose > 400 mg/dL or < 50 mg/dL
7. history of GI or urinary tract hemorrhage within past 21 days
8. post myocardial infarction pericarditis

Treatment protocol: Also, see *Contraindications*, page 1017.

Rx alteplase (Activase®): initiate < 4.5 hrs from onset of deficit. NINDS protocol: 0.09 mg/kg IV bolus over 1 min, followed by 0.81 mg/kg constant infusion over 60 minutes (up to a maximum of 90 mg total, including the bolus)[29].

HTN is aggressively controlled.

Anticoagulants and antiplatelet drugs are held for 24 hrs after treatment. If there is an indication for anticoagulation, obtain a non-contrast CT 24 hours prior to starting anticoagulation since there is a risk of subclinical intracerebral hemorrhage.

ICH following IV tPA

There is an increased risk of *symptomatic* intracerebral hemorrhage **(ICH)** with the use of tPA (NINDS study: 6.4% vs. 0.6% with placebo; ECASS II: 8.8% vs. 3.4%). In spite of this, the NINDS study found that mortality in the tPA

group was similar to controls at 3 mos (17% vs. 21%). The following factors were associated with an increased risk of symptomatic ICH (with only a 57% efficiency rate of predicting ICH): severity of NIHSS score, or pretreatment CT showing brain edema or mass effect. In one study, ICH did not influence outcome except in the rare instance when a massive hematoma occurred[37]. Outcomes were still better in the treated group, and the conclusion is that these patients are still reasonable candidates for tPA[38]. Since then, multicenter analyses have demonstrated that size of infarction and elevated blood sugar are independent risk factors for symptomatic ICH[39].

Management of post-tPA ICH:

1. discontinue tPA infusion of and obtain STAT head CT
2. send labs: PT, aPTT, platelet count, fibrinogen, and type & cross
3. prepare to administer 6-8 units cryoprecipitate containing Factor VIII
4. prepare to administer 6-8 units of platelets
5. if emergent EVD placement or other interventional procedure is needed, consider the use of recombinant Factor VIIa (40-80mg/kg) immediately beforehand (NB: this is only a temporizing measure and cryoprecipitate needs to still be given)

ENDOVASCULAR THERAPY FOR STROKE

Intraarterial tPA

May be employed up to 6 hours after stroke onset for patients ineligible for the IV protocol above (e.g. after the 4.5 hour window), as long as there is not a contraindication for tPA. For statistics with IA-tPA/stenting with total carotid occlusions, *see page 1157*.

MECHANICAL EMBOLECTOMY/CLOT DISRUPTION

MERCI retriever: Acronym: Mechanical Embolus Removal in Cerebral Ischemia. Nitinol corkscrew-shaped wire passed through angio catheter to pull out thrombus. An alternative for opening intracranial vessels for patients ineligible for intravenous tPA.

Use of the MERCI device **within 8 hours** of the onset of stroke symptoms in patients ineligible for intravenous tPA resulted in recanalization in 48% (68/141) (nonrandomized, multicenter prospective trial[40]). Clinically significant procedural complications occurred in 7.1% (10 of 141). Symptomatic

intracerebral hemorrhage occurred in 7.8% (11 of 141). Good neurological outcomes (modified Rankin score 2) were more frequent at 90 days in patients with successful recanalization compared with patients with unsuccessful recanalization (46% vs. 10%; relative risk [RR], 4.4; 95% CI, 2.1 to 9.3; P<0.0001), and mortality was less (32% vs. 54%).

Penumbra system: An aspiration catheter to remove thrombus with a separator wire used to macerate the clot and maintain catheter patency.

- 81.6% rate of revascularization (TIMI 2 or 3 flow) vs. 48.2% historical controls.
- 3.2% procedural serious adverse events vs. 7.1% historical control
- ICH: symptomatic ICH in 11.2%; asymptomatic ICH in 16.8%
- improvement ≥ 4 point in NIHSS at discharge in 57.8%
- modified Rankin Score (mRS) < 2 at 90 days achieved by 25% of patients

Balloon angioplasty and stenting: Stenting likely works by buttressing the clot. High efficacy reported in failure of other options.

EKOS ultrasound catheter: Combines clot softening using a distal catheter ultrasound transducer with infusion of a thrombolytic agent through the catheter.

MANAGEMENT OF PATIENTS NOT UNDERGOING THERAPY DIRECTED AT THROMBUS

These guidelines are for TIA or stroke, but not SAH (for this, *see page 1040*) nor intracerebral hemorrhage **(ICH)** (*see page 1126*)[41]. The following guidelines for initial management should be maintained 48 hrs after last neuro deterioration.

1. frequent VS with crani checks (q 1 hr **x** 12 hrs, then q 2 hrs)
2. activity: bed rest
3. labs:
   A. routine: CBC + platelet count, electrolytes, PT/PTT, U/A, EKG, CXR, ABG
   B. “special” (when appropriate): RPR (to rule-out neurosyphilis), ESR (to rule-out giant cell arteritis), hepatic profile, cardiac profile
   C. at 24 hrs: CBC, platelet count, cardiac profile, lipid profile, EKG
4. O_2 at 2 L per NC; repeat ABG on 2 L O_2
5. monitor cardiac rhythm **x** 24 hrs (literature quotes 5-10% prevalence of EKG changes, and 2-3% acute MIs in patients with stroke)
6. diet: NPO

7. nursing care
   A. indwelling Foley (urinary) catheter if consciousness impaired or if unable to use urinal or bedpan; intermittent catheterization q 4-6 hrs PRN no void if Foley not used
   B. accurate I's & O's; notify M.D. for urine output < 20 cc/hr **x** 2 hrs by Foley, or < 160 cc in 8 hrs if no Foley
8. IV fluids: NS or 1/2 NS at 75-125 cc/hr for most patients (to eliminate dehydration if present)
   A. <u>avoid glucose</u>: hyperglycemia may extend ischemic zone (penumbra)[42]. Although hyperglycemia may be a stress response and may not be neurotoxic[43], recommendations are to strive for normoglycemia[44]
   B. avoid overhydration in cases of ICH, CHF, or SBP > 180. It had been suggested that an optimal Hct for compromise between O_2 delivery and decreased viscosity was ≈ 33% and that fluid management should strive for this, however the early promise of this theory has not been borne out
9. treat CHF and arrhythmias (check CXR & EKG). MI or myocardial ischemia may present with neuro deficit, these patients should be admitted to CCU
10. avoid diuretics unless volume overloaded
11. blood pressure **(BP)** management:
    A. for patients presenting with HTN: management must take baseline BP into account: see *Hypertension in stroke patients* below for management
    B. for patients presenting with hypotension (SBP < 110 or DBP < 70):
       1. unless contraindicated (viz.: ICH, cerebellar infarct, or decreased cardiac output) give 250 cc NS over 1 hr, then 500 cc over 4 hrs, then 500 cc over 8 hrs
       2. if fluid ineffective or contraindicated: consider pressors
12. medications
    A. ASA 325 mg PO q d (unless hemorrhagic stroke proven or suspected)
    B. stool softener
13. see following sections for discussion of anticoagulation (*page 1020*), steroids (*page 1020*), and mannitol (*page 1020*)

HYPERTENSION IN STROKE PATIENTS

HTN may actually be needed to maintain CBF in the face of elevated ICP, and it usually resolves spontaneously. Therefore treat HTN cautiously and slowly to avoid rapid reduction and overshooting the target. Avoid treating mild HTN. Indications to treat HTN emergently include:

1. acute LV failure (rare)
2. acute aortic dissection (rare)
3. acute hypertensive renal failure (rare)
4. neurologic complications of HTN
   A. hypertensive encephalopathy
   B. converting a massive pale (ischemic) infarct into a hemorrhagic infarct
   C. patients with ICH (some HTN is needed to maintain CBF, see *Initial management of ICH*, page 1126)

Hypertension treatment algorithm (modified[41])

Recommended lower limits for treatment endpoints are shown in *Table 29-2*.

1. If DBP > 140 (malignant hypertension): ≈ 20-30% reduction is desirable. Cardene infusion or IV labetalol are agents of choice; arterial-line monitor recommended; sympatholytics (e.g. trimethaphan) contraindicated (they reduce CBF)
2. SBP > 230 or DBP 120-140 **x** 20 mins: <u>labetalol</u> (unless contraindicated, *see page 20*): start at 10 mg slow IVP over 2 mins, then double q 10 min (20, 40, 80, then 160 mg slow IVP) until controlled or total of 300 mg given. Maintenance: effective dose (from above) q 6-8 hrs PRN SBP > 180 or DBP > 110
3. SBP 180-230 or DBP 105-120: defer emergency treatment unless there is evidence of LV failure or if readings persist **x** 60 mins
   A. oral <u>labetalol</u> (unless contraindicated - *see page 20*) dosed as follows:
      1. for SBP > 210 or DBP > 110: 300 mg PO BID
      2. for SBP 180-210 or DBP 100-110: 200 mg PO BID
   B. if labetalol contraindicated:
      nifedipine start with 10 mg PO/SL, if still HTN after 1 hr, give 20 mg; then follow with 10-20 mg PO or SL q 6 hrs
   C. if monotherapy fails, or labetalol contraindicated, try either:
      • hydralazine (Apresoline®) 10 mg slow IVP q 6 hrs (**SIDE EFFECTS:** tachycardia, use with caution in ASHD)
      OR

• captopril (Capoten®) 6.25 mg, 12.5 mg or 25 mg PO q 8 hrs

4. SBP < 180 or DBP < 105: antihypertensive therapy usually not indicated

Table 29-2 Guidelines for lower limits of treatment endpoints for HTN in strokes

	No prior history of HTN	Prior history of HTN
do not lower **SBP** below	160-170 mm Hg	180-185 mm Hg
do not lower **DBP** below	95-105 mm Hg	105-110 mm Hg

Anticoagulants

Heparin: A prospective trial[45] administering continuous IV infusion of unfractionated heparin titrated to keep APTT 1.5-2.5 **x** control found no significant improvement in outcome[46]. The recurrent stroke rate in the 7 days following a stroke was only 0.6-2.2% per week[45, 47]. Effectiveness is unproven in strokes and TIAs except with cardiogenic brain embolism (see *Cardiogenic brain embolism*, page 1022). Anticoagulation may also be hazardous[48], however the complication rate has not been assessed prospectively (small, nonrandomized studies have found symptomatic ICH in 1-8%, and other bleeding complications in 3-12%[45]). Conversion rate of pale → hemorrhagic stroke is 2-5% (dog studies suggest the risk is increased only when HTN not well controlled). **Conclusion**: the risk of heparin therapy for acute focal cerebral ischemia exceeds any proven benefit[45], and is not justified in most cases (especially when used just to placate the frustrated clinician)[49, 50]. The American Heart Association has recommended: "Until more data are available, the use of heparin remains a matter of preference of the treating physician"[45]. A small but significant reduction in recurrent stroke has been shown with ASA.

Warfarin: High-intensity warfarin therapy has proven helpful for the antiphospholipid antibody syndrome **(APLAS)** (*see page 1025*).

For the rare indication for anticoagulation therapy:

1. first, R/O hemorrhage by CT before beginning therapy
2. ASA 325 mg PO q d in all patients with non-hemorrhagic stroke where anticoagulants or surgery not indicated
3. anticoagulants (heparin/warfarin):
    A. indications (rare)
        1. probably effective for cardiogenic emboli (see *Cardiogenic brain embolism* below)
        2. shown ineffective for stroke in evolution (neuro deficit that begins,

recurs, fluctuates, or worsens while patient in hospital), crescendo TIA[A] or completed stroke

3. unproven, but generally used for carotid dissection

B. contraindicated with large cardiac embolism, large stroke (risk of hemorrhagic conversion), pepticulcer disease that has bled in past 6 mos, uncontrolled severe HTN

C. start IV heparin and simultaneous warfarin (Coumadin®) (maintain heparin during first ≈ 3 days of warfarin because of initial hypercoagulability, see *Anticoagulation*, page 36 for target APTT and INR)

D. stop warfarin after 6 months (benefits decline, risks rise)

A. in 74 patients with recent TIAs, elevating PTT 1.5-2.5 **x** normal with heparin did not reduce recurrent TIAs nor strokes. Bleeding occurred in 9 (12.2%). Additional risk: hemorrhage from heparin induced thrombocytopenia[51]

DEXAMETHASONE (DECADRON®) AND STEROIDS

Indications:

1. steroid responsive vasculitis, e.g. giant cell arteritis (temporal arteritis)
2. cerebellar infarct/bleed with mass effect

MANNITOL

1. indicated for cerebellar infarct/bleed, prior to surgery, or if mass effect
2. contraindicated in hypotension
3. initial dose: 50 to 100 gm IV over 20 minutes

EMERGENCY SURGERY

Possible indications:

1. herniation from subdural hematoma
2. suboccipital craniectomy for progressive neurologic deterioration due to brainstem compression from cerebellar hemorrhage/infarction (*see below*)
3. decompressive craniectomy for malignant MCA territory stroke (*see below*)
4. carotid endarterectomy for high grade carotid stenosis ipsilateral to fluctuating neuro deficit (see *Emergency carotid endarterectomy*, page

1156)

CEREBELLAR INFARCTION

Relatively rare (seen on only 0.6% of all CTs obtained for any reason[52]). Cerebellar infarcts may be classified as involving the PICA distribution (cerebellar tonsil and/or inferior vermis), superior cerebellar artery distribution (superior hemisphere or superior vermis), or other indeterminate patterns[53]. 80% of patients developing signs of brainstem compression will die, usually within hours to days.

Early findings

In most cases the onset is sudden, without premonitory symptoms[54]. The first 12 hrs after onset were characterized by lack of progression. Early findings are due to the intrinsic cerebellar lesion (ischemic infarction or hemorrhage):

1. symptoms
   A. dizziness or vertigo
   B. nausea/vomiting
   C. loss of balance, often with a fall and inability to get up
   D. headache (infrequent in one series[54])
2. signs
   A. truncal and appendicular ataxia
   B. nystagmus
   C. dysarthria

Later findings

Patients with cerebellar infarction may subsequently develop increased pressure within the posterior fossa (due to cerebellar edema or mass effect from clot), with brainstem compression (particularly posterior pons). Clinical findings generally increase between 12-96 hrs following onset.

Surgical indications

Surgical decompression (*see below*) should probably be done as soon as any of the following signs develop[A] if there is no response to medical therapy[55]. Findings proceed in the approximate following sequence if there is no

intervention:

1. abducens (VI) nerve palsy
2. loss of ipsilateral gaze (compression of VI nucleus and lateral gaze center)
3. peripheral facial nerve paresis (compression of facial colliculus)
4. confusion and somnolence (may be partly due to developing hydrocephalus)
5. Babinski sign
6. hemiparesis
7. lethargy
8. small but reactive pupils
9. coma
10. posturing→ flaccidity
11. ataxic respirations

A. it is important to recognize a lateral medullary syndrome **(LMS)** (*see page 1028*) which may often accompany a cerebellar infarct. With LMS, the signs are usually present from the onset (dysphagia, dysarthria, Horner's syndrome, ipsilateral facial numbness, crossed sensory loss…), and are not accompanied by a change in sensorium. There is no place for surgical decompression in LMS since it represents primary brainstem ischemia and not compression

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Imaging studies

CT scan: may be normal very early in these patients. There may be subtle findings of a tight posterior fossa: compression or obliteration of basal cisterns or 4th ventricle.

MRI: (including DWI) more sensitive for ischemia, especially in the posterior fossa.

Suboccipital craniectomy for cerebellar infarction

Unlike the situation with *supra* tentorial masses causing herniation, there are several reports of patients in deep coma from direct brainstem compression who were operated upon quickly who made useful recovery[55-57]. Guidelines for patients with cerebellar *hemorrhage* appear on page 1130.

The operation of choice is a suboccipital decompression to include enlargement of the foramen magnum. The dura is then opened and the infarcted cerebellar tissue usually exudes "like toothpaste" and is easily aspirated. Avoid

using ventricular drainage alone as this may cause upward cerebellar herniation (*see* *page 285*) and does not relieve the direct brainstem compression.

29.2.4.1. Malignant middle cerebral artery territory infarction

A distinct syndrome that occurs in up to 10% of stroke patients[58, 59], which carries a mortality of up to 80% (mostly due to severe postischemic cerebral edema → increased ICP → herniation)[59].

Patients usually present with findings of severe hemispheric stroke (hemiplegia, forced eye and head deviation) often with CT findings of major infarct within the first 12 hours. Most develop drowsiness shortly after admission. There is progressive deterioration during the first 2 days, and subsequent transtentorial herniation usually within 2-4 days of stroke. Fatalities are often associated with: severe drowsiness, dense hemiplegia, age > 45-50 yrs[60], early parenchymal hypodensity involving > 50% of the MCA distribution on CT scan[61], midline shift > 8-10 mm, early sulci effacement and hyperdense artery sign[60] (*see* *page 1013*) in MCA.

Neurosurgeons may become involved in caring for these patients because aggressive therapies in these patients may reduce morbidity and mortality. Options include:

1. conventional measures to control ICP (with or without ICP monitor): mortality is still high, and elevated ICP is not a common cause of initial deterioration
2. hemicraniectomy (decompressive craniectomy): *see below*
3. ✖ to date, the following treatments have not improved outcome: agents to lyse clot, hyperventilation, mannitol, or barbiturate coma

Hemicraniectomy for malignant MCA territory infarction

May reduce mortality to as low as 32% in nondominant hemisphere strokes[62] (37% in all comers[63]) with surprising reduction of hemiplegia, and in dominant hemisphere strokes, with only mild-moderate aphasia (better results occur with early surgery, especially if surgery is performed before any changes associated with herniation occur). Meta-analysis[64] of 3 randomized controlled trials found that hemicraniectomy within 48 hours after stroke onset resulted in decreased mortality and increased the number of patients with a favorable functional outcome.

Indications: No firm indications. Guidelines:

1. age < 70 years
2. more strongly considered in nondominant hemisphere (usually right)
3. clinical & CT evidence of acute, complete ICA or MCA infarcts and direct signs of impending or complete severe hemispheric brain swelling (severe post-admission neurologic deterioration is the usual event that triggers surgical intervention)

Technique: *see page 165*.

29.2.5. Cardiogenic brain embolism

About one stroke in six is cardioembolic. Emboli may be composed of fibrin-rich thrombi (e.g. mural thrombi due to segmental myocardial hypokinesis following MI or ventricular aneurysm), platelets (e.g. nonbacterial thrombotic endocarditis), calcified material (e.g. in aortic stenosis), or tumor particles (e.g. atrial myxoma).

Following acute myocardial infarction (AMI): 2.5% of patients will have a stroke within 1-2 weeks of an AMI (the period when most emboli occur). The risk is higher with anterior wall MI (≈ 6%) vs. inferior wall MI (≈ 1%).

Atrial fibrillation (A-fib): Nonrheumatic patients with a-fib have a 3-5 fold increased risk of stroke[65], with a 4.5% rate of stroke per year without treatment[66]. The incidence of a-fib in the U.S. is 2.2 million. About 75% of strokes in patients with A-fib are due to left atrial thrombi[67]. Independent risk factors for stroke in patients with A-fib are: advanced age, prior embolism (stroke or TIA), HTN, DM, and echocardiographic evidence of left atrial enlargement or left ventricular dysfunction[65].

The CHADS2 scoring system for patients with a-fib has been widely validated[68] and is shown in *Table 29-3*. The points are totalled and risk assessment is shown in *Table 29-4*. For patients with a CHADS2 score ≥ 2, warfarin therapy was significantly protective for out-of-hospital death or hospitalization for stroke, MI or hemorrhage (CI = 0.61-0.91)[69].

Prosthetic heart valves: Patients with mechanical prosthetic heart valves on long-term anticoagulation have an embolism rate of 3%/year for mitral and 1.5%/year for aortic valves. With bioprosthetic heart valves and no anticoagulation the risk is 2-4%/year.

Paradoxical embolism: Paradoxical embolism can occur with a patent foramen ovale which is present in 10-18% of the general population, but in up to 56% of young adults with unexplained stroke[70].

Endocarditis: Blood cultures and TEE help evaluate.

Table 29-3 CHADS2 scoring items

Item	Points
CHF (any history)	1
HTN (prior history)	1
Age > 75 yrs	1
Diabetes mellitus	1
Secondary prevention: in patients with prior ischemic stroke or TIA; most also include systemic embolic events	2

Table 29-4 Risk based on CHADS2 score

CHADS 2 score	Annual stroke risk (%/year)
0	1.9
1	2.8
2	4
3	5.9
4	8.5
5	12.5
6	18.2

DIAGNOSIS

No specific neurologic features can distinguish these patients. The diagnosis is suggested in imaging studies showing multiple intracranial ischemic strokes in different arterial distributions, the differential diagnosis includes: vasculitis, intracranial atherosclerosis (focal plaques, more common in Asian populations that consume Western diets), and intravascular lymphomatosis.

The diagnosis of cardiogenic brain embolism **(CBE)** as a cause of a stroke relies on demonstrating a potential cardiac source, the absence of cerebrovascular disease, and non-lacunar stroke.

Large areas of hemorrhagic transformation within an ischemic infarct may be more indicative of CBE due to thrombolysis of the clot and reperfusion of infarcted brain with subsequent hemorrhagic conversion. Hemorrhagic transformation most often occurs within 48 hrs of a CBE stroke, and is more

common with larger strokes.

Detection of cardiac source

Most centers rely on echocardiography (without transesophageal ability). Using restricted criteria (i.e. excluding mitral valve prolapse), about 10% of patients with ischemic stroke will have potential cardiac source detected by echo, and most of these patients have other manifestations of cardiac disease. In stroke patients without clinical heart disease, only 1.5% will have a positive echo; the yield is higher in younger patients without cerebrovascular disease[71].

EKG may detect atrial fibrillation which may be seen in 6-24% of ischemic strokes, and may be associated with a 5-fold increased risk of stroke (*see below*).

Treatment

CBE is essentially the only condition for which anticoagulation has been shown to significantly reduce the rate of further strokes.

One must balance the risk of recurrent emboli (12% of patients with a cardioembolic stroke will have a second embolic stroke within 2 weeks) against that of converting a pale infarct into a hemorrhagic one. No study has shown a clear benefit of early anticoagulation.

Recommendations for anticoagulation:

1. if anticoagulation is to be used, it should not be instituted within the first 48 hrs of a probable CBE stroke
2. CT should be obtained after 48 hrs following a CBE stroke and before starting anticoagulation (to R/O hemorrhage)
3. anticoagulation should not be used in the face of large infarcts
4. start heparin and warfarin simultaneously. Continue heparin for 3 days into warfarin therapy (see *Anticoagulation*, page 36)
5. optimal range of oral anticoagulation to minimize subsequent embolism and/or hemorrhage has not been determined, but pending further data, an INR of 2-3 appears satisfactory
6. patients with asymptomatic A-fib have 66-86% reduction in stroke risk with warfarin (Coumadin®)[65, 72]. ASA is only about half as effective, but may be sufficient for those without associated risk factors (listed on page 1022)[65]

29.3. Stroke in young adults

Only 3% of ischemic strokes occur in patients < 40 yrs age[73]. Over 10% of ischemic strokes occur in patients ≤ 55 yrs[74]. Incidence: 10 per 100,000 persons age 35-44 yrs[75], 73 per 100,000 for age < 55 yrs[74].

Etiologies

The differential diagnosis is lengthy[73], with trauma being the most common cause of strokes (22%) in patients under 45 yrs[76]. Most of the rest are covered by the small number of etiologies listed below (excludes: trauma, post-op stroke, SAH, and intracerebral hemorrhage).

1. **atherosclerosis**: 20% (all 18 patients in one series had either ID-DM, or were males > 35 yrs with ≥ 1 risk factors (*see below*), most had TIAs earlier)
2. **embolism** with recognized source: 20%
   A. cardiac origin is the most common (see *Cardiogenic brain embolism* above), most have previously known cardiac disease:
      1. rheumatic heart disease
      2. prosthetic valve
      3. endocarditis
      4. mitral valve prolapse **(MVP)**: present in 5-10% of young adults, in 20-40% of young adults with stroke (although one series found MVP in only 2% of stroke in young adults[75])
      5. A-fib
      6. left-atrial myxoma

   B. fat embolism syndrome: neurologic manifestation is usually global neurologic dysfunction

   C. paradoxical embolism: ASD, pulmonary AVM including Osler-Weber-Rendu syndrome, patent foramen ovale (see *Cardiogenic brain embolism* above)

   D. amniotic fluid embolism: may occur typically in the post-partum period
3. **vasculopathy**: 10%
   A. inflammatory
      1. Takayasu's
      2. infective: TB, syphilis, ophthalmic zoster
      3. amphetamine abuse
      4. herpes zoster ophthalmicus **(HZO)**: usually presents with delayed

contralateral hemiplegia with a mean of ≈ 8 weeks following HZO[77]

5. mucormycosis: a nasal and orbital fungal infection primarily in diabetics and immunocompromised patients that causes an arteritis which may thrombose the orbital veins and ICA or ACA. Produces proptosis, ocular palsy, and hemiplegia (*see page 836*)
6. associated with systemic disease
   a. SLE (lupus) (also *see below* under *Coagulopathy*)
   b. arteritis (especially periarteritis nodosa, *see page 77*): when confined to CNS is usually multifocal and progressive, but may mimic stroke early
   c. multiple sclerosis **(MS)**
   d. cancer
   e. rheumatoid arthritis

B. non-inflammatory
   1. fibromuscular dysplasia: *see page 79*
   2. carotid or vertebral artery dissections (including posttraumatic)
   3. moyamoya disease: *see page 1170*
   4. **homocystinuria**: a genetic defect in methionine metabolism that produces intimal thickening and fibrosis in almost all vessels with associated thromboembolic events (arterial and venous, including dural venous sinuses). Estimated risk of stroke is 10-16%. Patients have a Marfan syndrome-like physical appearance, malar blotches, mental retardation, and elevated levels of urinary homocysteine
   5. pseudoxanthoma elasticum

4. **coagulopathy**: 10%. The following are associated with hypercoagulable states
   A. SLE: lupus anticoagulant → prolonged PTT incompletely corrects with 50/50 mix. Collagen vascular disease only rarely presents initially with stroke
   B. polycythemia or thrombocytosis
   C. sickle cell disease
   D. TTP (thrombotic thrombocytopenic purpura)
   E. antithrombin III deficiency (controversial - not seen in large series of young adults with stroke)
   F. protein C or protein S deficiency (familial): protein C attenuates hemostatic reactions, homozygous deficiency is fatal in the neonatal period. Heterozygous deficiency is associated with thrombotic strokes.

A rare complication during initial therapy with warfarin is a drop in protein C before other coagulation factors resulting in a hypercoagulable state

   G. **antiphospholipid-antibody syndrome (APLAS)**[78, 79]: causes venous and/or arterial thrombosis. The two best known antiphospholipid-antibodies are anticardiolipin antibodies **(ACLA)**, and lupus anticoagulant **(LAC)**. Once they become symptomatic, treatment is high-intensity warfarin therapy to an INR ≥ 380. There is a dramatic increase in thrombotic events after discontinuing warfarin. Aspirin is useless

   H. following use of the drug 3,4-methylenedioxymethamphetamine (**MDMA**, known on the street as ecstasy)[81], possibly independent of the hypercoagulable state that occurs with hyperthermia when insufficient fluids are consumed in conjunction with use of the drug

5. **peripartum**: 5% (usually within 2 wks of parturition)
6. miscellaneous causes: 35%
   A. uncertain etiology

   B. oral contraceptives **(BCP)**: associated with ninefold increased risk for stroke, many with prior migraine history

   C. venous thrombosis (including dural sinus thrombosis): incidence may be increased with use of BCP

   D. **migraine** 82: widely accepted, but difficult to assess objectively (incidence of stroke in these patients may be same as general population). <u>Rare</u>. Usually occurs in women, with a benign long-term course; recurs in < 3%. Possible mechanisms include: vasospasm, platelet dysfunction and arteriopathy[83]. strokes often occur during a migrainous attack[84] or shortly thereafter

   E. cocaine abuse[85]: stroke may result from vasoconstriction, or from HTN in the presence of aneurysms or AVMs (frank vasculitis occurs[86] but is rare with cocaine, unlike amphetamines); strokes with alkaloidal cocaine ("crack") are ≈ equally divided between ischemic and hemorrhagic

   F. posterior reversible encephalopathy syndrome **(PRES)**: *see page 73*

Risk factors

In a retrospective "neighborhood control" study of 201 Australian patients aged 15-55 (mean = 45.5) with first-time strokes, the following risk factors were

identified[74]:

1. diabetes: odds ratio = 12
2. HTN: odds ratio = 6.8
3. current cigarette smoking: odds ratio = 2.5
4. long-term heavy alcohol consumption: odds ratio = 15 (heavy alcohol ingestion within 24 hrs preceding the stroke was not a risk factor)

EVALUATION

1. history & physical exam directed at uncovering systemic disease (*see above*) and modifiable risk factors (*see above*)
2. cardiology work-up including EKG and echocardiogram
3. bloodwork (include as appropriate):
   A. routine: electrolytes, CBC, platelet count and/or function, ESR (elevation may suggest SLE, arteritis, atrial myxoma… but a normal ESR does not rule-out vasculitis), PT/PTT, VDRL (should be obtained in all young adults with stroke), fasting lipid profile
   B. for unexplained stroke: ANA, antithrombin III, protein C, protein S, homocysteine, factor V Leiden, PPD, sickle-cell screen, toxicology screen (blood and urine, to R/O drugs such as cocaine), SPEP, lupus anticoagulant, serum amino acid, tissue plasminogen-activator and -inhibitor
4. miscellaneous tests: U/A, CXR, CSF exam when indicated
5. cerebral angiography: not always necessary for patients with obvious systemic disease or strong evidence for cardiac embolism; may occasionally diagnose cerebral embolism if performed within 48 hrs of ictus

29.4. Lacunar strokes

Small infarcts in deep noncortical cerebrum or brain-stem (*see Table 29-5*) resulting from occlusion of penetrating branches of cerebral arteries. Size of infarcts ranges from 3-20 mm (CT detects larger ones; better sensitivity in white matter).

Small (3-7 mm) lacunes may be due to **lipohyalinosis** (vasculopathy due to HTN) of arteries < 200 microns (may also be cause of many ICHs); this vasculopathy is indicative of small vessel disease, unlikely to be prevented by

carotid endarterectomy.

Clinically, diagnosis virtually excluded by: aphasia, apractagnosia, sensorimotor stroke, monoplegia, homonymous hemianopsia **(HH)**, severe isolated memory impairment, stupor, coma, LOC, or seizures.

L'etat lacunaire: multiple lacunes → chronic progressive neuro decline with one or more episodes of hemiparesis; results in invalidism, dysarthria, small-step gait (marche á petits pas), imbalance, incontinence, pseudobulbar signs, dementia. Many signs and symptoms are possibly due to NPH (unrecognized originally).

Table 29-5 Typical locations for lacunar strokes (in descending frequency)

- putamen
- caudate
- thalamus
- pons
- internal capsule (IC)
- convolutional white matter

LACUNAR SYNDROMES

Major syndromes (see reference[87] for others):

1. **pure sensory stroke or TIA**: (the most common lacunar manifestation) usually isolated unilateral numbness of face, arm, and leg. Only 10% of TIA go on to stroke. Lacune in sensory (posteroventral) thalamus → CT detection is poor. **Dejerine-Roussy** = rare thalamic pain syndrome that may develop late
2. **pure motor hemiparesis (PMH)**: (2nd most common lacunar manifestation) pure unilateral motor deficit of face, arm and leg without sensory deficit, HH, etc.. Lacune in posterior limb of IC, or in lower basis pontis where corticospinal **(CS)** tracts coalesce, or rarely in mid-cerebral peduncle
3. **ataxic hemiparesis**: contralateral PMH + cerebellar ataxia of affected limbs (if they can move). Lacune in basis pontis at junction of upper third and lower two thirds → dysarthria, nystagmus and unidirectional toppling possible. Differential severity in face, arm and leg possible because CS fibers dispersed by nuclei pontis (unlike compact pyramids and peduncle)
    A. variant: dysarthria-clumsy hand syndrome: lesion in same location or genu of IC. May be mimicked by a cortical infarct, but latter will have numb lips

4. **PMH sparing the face**: lacune in medullary pyramid; at onset, there may be vertigo and nystagmus (approaching lateral medullary syndrome)
   A. variant: thalamic dementia: central region of one thalamus + adjacent subthalamus → abulia, memory impairment + partial Horner's (miosis + anhidrosis)
5. **mesencephalothalamic syndrome**: "**top o' the basilar syndrome**". Usually caused by embolus. Infarct typically butterfly shaped & bilateral involving rostral brainstem and cerebral hemisphere regions fed by the distal basilar artery. Clinical: III palsy, **Parinaud's syndrome** & abulia, may have amnesia, hallucinations and somnolence, usually without significant motor dysfunction
6. **Weber's syndrome**: Cr. N. III palsy with contralateral PMH (no sensory loss). Usually due to occlusion of interpeduncular branches of basilar artery → central midbrain infarction, disrupting cerebral peduncle and issuing fibers of III. May also be due to aneurysm of basilar bifurcation or BA-SCA junction
7. PMH with crossed VI palsy: lacune in paramedian inferior pons
8. cerebellar ataxia with crossed III palsy (Claude syndrome): lacune in dentatorubral tract (superior cerebellar peduncle)
9. **hemiballism**: classically, infarct or hemorrhage in subthalamic semilunar nucleus of Luys
10. lateral medullary syndrome: *see below*
11. **locked-in syndrome**: bilateral PMH from infarct at IC, pons, pyramid or (rarely) cerebral peduncles

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29.5. Collateral circulation

COLLATERAL CIRCULATION FOR ICA STENOSIS/OCCLUSION

The effects of ICA stenosis/occlusion may be ameliorated by collateral blood flow. Potential alternate routes for blood to reach brain tissue include:

1. flow through the circle of Willis
   A. from contralateral ICA through anterior communicating a.
   B. from forward flow through the ipsilateral posterior communicating a.
2. retrograde flow through <u>ophthalmic a.</u> parasitizing blood from <u>both</u> ECAs via:
   A. facial a. → angular a. → dorsal nasal a. & medial palpebral a.

B. maxillary a.
1. middle meningeal a. → lacrimal a.
2. vidian a. (a. of the pterygoid canal)
C. transverse facial a. → lateral palpebral a.
D. superficial temporal a. → supraorbital a.
3. proximal maxillary a. → anterior tympanic a. → caroticotympanic branch of ICA
4. cortical-cortical anastomoses
5. dural-leptomeningeal anastomoses

COLLATERAL CIRCULATION FOR VERTEBROBASILAR STENOSIS/OCCLUSION

Available collaterals depend on the site of occlusion.

Basilar artery occlusion. Collateral flow via:
1. posterior communicating aa.
2. anastomoses between SCA and PICA

Proximal vertebral artery **(VA)** occlusion. Collateral flow via:
1. ECA → occipital a. → muscular branches of VA → VA
2. thyrocervical trunk → ascending cervical a. → direct connection or spinal radicular aa. → VA
3. contralateral VA and/or ascending cervical a. via spinal radicular branches and anterior spinal artery

29.6. "Occlusion" syndromes

See *Figure 5-15*, page 96 for the distribution territories of the major cerebral arteries. Organized by vascular territories[A]
1. internal carotid artery: risk and extent of stroke is influenced by suddenness of occlusion, location of occlusion, and collateral circulation (*see above*)
   A. statistics:
   1. *acute* ICA occlusion (all comers): 26-49% risk of stroke[88] (not all of these strokes are severe)
   2. annual stroke risk in 1261 patients with *symptomatic* ICA

occlusion: 7% overall, 5.9% ipsilateral to the occlusion (mean follow-up = 45.5 mos) (12 prospective studies[89])

3. stroke risk is less when one includes *asymptomatic* ICA occlusions
4. in patients presenting with ICA territory stroke or TIA, complete ICA occlusion is found in 10-15%[90]

B. worst-case scenario of total ICA occlusion with no a-comm or p-comm flow and no collateral rescue: stroke in ACA and MCA territories

2. middle cerebral artery*

	complete (M1 occlusion)	superior division	inferior division
A. {CL} weakness of UE > LE	X	X	
B. {CL} weakness of lower face	X	X	
C. {CL} hemisensory loss (UE & LE)	X	X	
D. {CL} hemisensory loss face (all modalities)	X	X	
E. {CL} neglect†	X	X	
F. {IL} gaze preference	X		
G. {CL} homonymous hemianopsia	X		X‡
H. receptive aphasia§ (Wernicke's area)	X		X
I. expressive aphasia§ (Broca's area)	X	X	
J. Gerstmann syndrome: with dominant parietal lobe infarct (*see page 113*)			

* an "X" indicates that the deficit is present
† with involvement on side of nondominant hemisphere
‡ plus {CL} upper quadrantanopsia
§ with involvement on the side of the dominant hemisphere

3. anterior cerebral artery: {CL} weakness of LE > UE
4. posterior cerebral artery
   A. unilateral occipital lobe infarction → homonymous hemianopsia with macular sparing (visual cortex of the macula receives dual blood supply from MCA and PCA)
   B. Balint syndrome
   C. cortical blindness (Anton syndrome)
   D. Weber syndrome
   E. alexia without agraphia
   F. thalamic pain syndrome (Dejerine-Roussy syndrome)
5. artery of Percheron (*see page 104*): bilateral thalamic and mesencephalic infarctions[91]
6. vertebral artery
   A. medial medullary syndrome (Dejerine syndrome)
   B. lateral medullary syndrome (Wallenberg syndrome): *see below*
7. basilar artery

8. AICA: lateral pontine syndrome (Marie-Foix syndrome)
9. PICA: sometimes lateral medullary (Wallenberg) syndrome: *see below*
10. SCA: infarction of superior cerebellar vermis and superior cerebellum
11. anterior spinal artery
12. **recurrent medial striate artery** (of Heubner): expressive aphasia + mild hemiparesis (UE > LE, proximal muscles weaker than distal)
13. **anterior choroidal artery (AChA)** syndrome: the complete triad consists of {CL} hemiplegia, hemihypesthesia and homonymous hemianopsia (mnemonic: 3 H's), however, incomplete forms are more common[92]. Occlusion is usually due to small vessel disease and CT or MRI usually shows infarct in posterior limb of IC (just above temporal horn of lateral vent)[93] and white matter posterior and lateral to it. Occlusion is usually tolerated fairly well, and ligation of this artery was actually utilized in treatment of Parkinsonism sometimes without ill effect[94] (p 540) (see *Surgical treatment of Parkinson's disease*, page 532) but internal capsule infarct occurred in ≈ 15%.

A. to indicate lateralization of findings, {CL} = contralateral, {IL} = ipsilateral

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Lateral medullary syndrome (LMS)

AKA **Wallenberg's syndrome**, AKA PICA syndrome. Classically attributed to PICA occlusion, but in 80-85% of cases the vertebral artery is also involved[95]. No cases have been reported arising from brainstem hemorrhage. Onset is usually acute. The findings are listed in *Table 29-6* (NB: absence of pyramidal tract findings, and no change in sensorium).

The location of the lesion and medullary structures are shown in *Figure 29-1*. This is essentially the only location where a lesion will produce sensory loss on one side of the face (ipsilateral to the lesion) and contralateral sensory loss in the body. All in the absence of pyramidal tract findings (i.e. overt weakness).

Table 29-6 Findings in lateral medullary syndrome[94] (p 547)

GENERALIZED symptoms	Responsible lesion
• vertigo, N/V, nystagmus, diplopia, oscillopsia	vestibular nuclei & connections

• hiccups	?
IPSILATERAL to lesion	**Responsible lesion**
• facial pain, paresthesias, & impaired sensation	descending tract and nucleus V over half of face
• ataxia of limbs	(restiform body?)
• Horner’s syndrome	descending sympathetic tract
• dysphagia, diminished gag, hoarseness	exiting fibers of IX & X
• numbness of arm, trunk, or leg	cuneate & gracile nuclei
CONTRALATERAL to lesion	**Responsible lesion**
• impaired pain & temp sense over half of body	spinothalamic tract

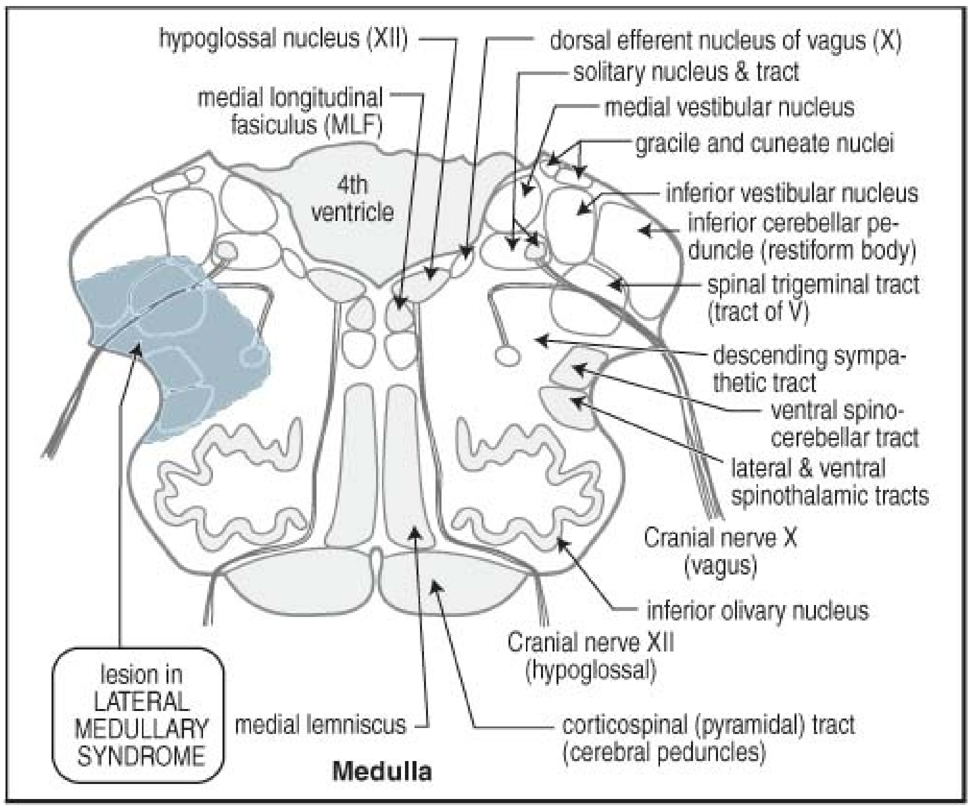

Figure 29-1 Typical lesion in lateral medullary syndrome (indicated as shaded area)

These patients sometimes develop severe cerebellar swelling that responds to neurosurgical decompression (the tissue aspirates easily) (*see page 1022*).

In a patient presenting with LMS, one needs to rule-out vertebral dissection (*see page 1163*) since this would be treated with heparin. MRI including fat-suppressed T1WI and MRA would detect dissection in most cases.

Prognosis: 12% of 43 patients died during the acute phase from respiratory and

cardiovascular complications and 2 new posterior-fossa strokes occurred[96]. Recurrent vertebrobasilar territory stroke rate was 1.9% per year[96].

29.7. Miscellaneous stroke

WATERSHED INFARCT

An ischemic infarction in a territory located at the periphery of two bordering arterial distributions due to a disturbance in flow in one or both of the arteries.

EMOTIONAL INCONTINENCE

AKA emotionalism or emotional lability[97]. Usually consists of uncontrollable fits of crying or laughter in response to minor events. Generally without emotional content. Described with a variety of lesions in the cortex, diencephalon, and brainstem, but usually involving systems controlling motor function (pyramidal or extrapyramidal fibers) and an interruption of a control system purportedly located at the base of the brainstem. May respond to SSRI therapy (e.g. paroxetine)[92].

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NOTES

30. SAH and aneurysms

30.1. Introduction to SAH

Etiologies

Etiologies of subarachnoid hemorrhage **(SAH)** include[1]:

- trauma: the most common cause of SAH[2, 3]
- "spontaneous SAH"
  - A. ruptured intracranial aneurysms: 75-80% of spontaneous SAHs (*see page 1055*)
  - B. cerebral arteriovenous malformation (AVM): 4-5% of cases (AVMs more commonly cause ICH & IVH than SAH - *see page 1099*)
  - C. certain vasculitides that involve the CNS (see *Vasculitis and vasculopathy*, page 74)
  - D. rarely due to tumor (many case reports[4-15])
  - E. cerebral artery dissection (may also be post-traumatic)
    - carotid artery: *see page 1162*
    - vertebral artery: may cause intraventricular blood (especially 4th and third ventricle), *see page 1163*
  - F. rupture of a small superficial artery
  - G. rupture of an infundibulum (*see page 1039*)
  - H. coagulation disorders:
    - iatrogenic or bleeding dyscrasias
    - thrombocytopenia
  - I. dural sinus thrombosis
  - J. spinal AVM: usually cervical or upper thoracic (*see page 507*)
  - K. pretruncal nonaneurysmal SAH: *see page 1085*
  - L. rarely reported with some drugs: e.g. cocaine (*see page 276*)
  - M. sickle cell anemia
  - N. pituitary apoplexy: *see page 635*
  - O. no cause can be determined in 14-22% (see *SAH of unknown etiology*,

page 1083)

Incidence

Estimated annual rate of aneurysmal SAH in most western populations: 6-8 per 100,000 population[16, 17].

Outcome of aneurysmal SAH

- 10-15% of patients die before reaching medical care
- mortality is 10% within first few days
- 30-day mortality rate was 46% in one series[16], and in others over half the patients died within 2 weeks of their SAH[18]
- overall mortality is ≈ 45% (range: 32-67%)[19]
- causes of mortality
    - 25% die as a result of medical complications of SAH[20]
        - neurogenic pulmonary edema: *see page 28*
        - neurogenic stunned myocardium: *see page 1054*
    - about 8% die from progressive deterioration from the initial hemorrhage[21 (p 27)]
- among patients surviving the initial hemorrhage treated without surgery, rebleeding is the major cause of morbidity and mortality (*see page 1043*), the risk is ≈ 15-20% within 2 weeks. The goal of early surgery (see *Timing of aneurysm surgery*, page 1060) is to reduce this risk
- of those reaching neurosurgical care, vasospasm (*see page 1045*) kills 7%, and causes severe deficit in another 7%[22]
- about ≈ 30% of survivors have moderate to severe disability[19]
- ≈ 66% of those who have successful aneurysm clipping never return to the same quality of life as before the SAH[19, 23]
- patients ≥ 70 yrs age fare worse for each neurologic grade[24]

Miscellaneous facts about SAH

- peak age for aneurysmal SAH is 55-60 years, ≈ 20% of cases occur between ages 15-45 yrs[25]
- 30% of aneurysmal SAHs occurs during sleep
- 50% of patients with aneurysms have warning symptoms, usually 6-20 days

before SAH[26] (see *Presentation other than major rupture*, page 1056)
- headache is lateralized in 30%, most to the side of the aneurysm
- SAH is complicated by intracerebral hemorrhage in 20-40%, by intraventricular hemorrhage in 13-28% (*see page 1056*), and by subdural blood in 2-5% (usually due to p-comm aneurysm when over convexity, or distal anterior intracerebral artery (DACA) aneurysm with interhemispheric subdural (*see page 1068*))
- soft evidence suggests that rupture incidence is higher in spring and autumn
- patients ≥ 70 yrs age have a higher proportion with a severe neurologic grade[24]

Risk factors for SAH[1]

- hypertension
- oral contraceptives
- substance abuse
  - cigarette smoking[27]
  - following cocaine abuse: *see page 276*
  - alcohol consumption[28]: controversial[29]
- diurnal variations in blood pressure[30]
- pregnancy and parturition (see *Pregnancy & intracranial hemorrhage*, page 1086)
- slight increased risk during lumbar puncture and/or cerebral angiography in patient with cerebral aneurysm
- slight increased risk with advancing age[16]
- conditions with an increased incidence of cerebral aneurysms (*see page 1057*)

CLINICAL FEATURES

SYMPTOMS OF SAH

Sudden onset of severe H/A (*see below*), usually with vomiting, syncope (apoplexy), neck pain (meningismus), and photophobia. If there is LOC, patient may subsequently recover consciousness[31]. Focal cranial nerve deficits may occur (e.g. third nerve palsy from aneurysmal compression, causing diplopia and/or ptosis). Low back pain may develop due to irritation of lumbar nerve roots by dependent blood.

Headache

The most common symptom, present in up to 97% of cases. Usually severe (classic description: “the worst headache of my life”) and sudden in onset. They may clear and the patient may not seek medical attention (referred to as a **sentinel hemorrhage** or headache, or **warning headache**; they occur in 30-60% of patients presenting with SAH). If severe or accompanied by reduced level of consciousness, most patients present for medical evaluation. Patients with H/A due to minor hemorrhages will have blood on CT or LP. However, warning headaches may also occur without SAH and may be due to aneurysmal enlargement or to hemorrhage confined within the aneurysmal wall[32]. Warning H/A are usually sudden in onset, severe, and clear within 1 day.

Differential diagnosis of severe, acute, paroxysmal headache (25% will have SAH[33]):

1. subarachnoid hemorrhage, AKA “warning headache” or sentinel H/A (*see above*)
2. benign “**thunderclap headaches**” **(BTH)** or crash migraine[34]. Severe global headaches of abrupt onset that reach maximal intensity in < 1 minute, accompanied by vomiting in ≈ 50%. They may recur, and are presumably a form of vascular headache. Some may have transient focal symptoms. There are no clinical criteria that can reliably differentiate these from SAH[35]. There is no subarachnoid blood on CT and LP, which should probably be performed on at least the first presentation to R/O SAH. Earlier recommendations to angiogram these individuals[36] have since been tempered by experience[37, 38]
3. reversible cerebral vasoconstrictive syndrome **(RCVS)**[39] (AKA benign cerebral angiopathy or vasculitis[40]): severe H/A with paroxysmal onset, ± neurologic deficit, and string of beads appearance on angiography of cerebral vessels that usually clears in 1-3 months. > 50% report prior use of vasoconstrictive substances (cocaine, marijuana, nasal decongestants, ergot derivatives, SSRIs, interferon, nicotine patches) sometimes combined with binge drinking. May also occur post-partum. Complications occurred in 24% including:
   A. usually during the 1st week: SAH, ICH, seizures, RPLS
   B. usually during the 2nd week: ischemic events (TIA, CVA)
4. **benign orgasmic cephalgia**: a severe, throbbing, sometimes “explosive” H/A with onset just before or at the time of orgasm (distinct from pre-

orgasmic headaches which intensify with sexual arousal[41]). In a series of 21 patients[42] neurologic exam was normal in all, and angiography done in 9 was normal. 9 had a history of migraine in the patient or a family member. No other symptoms developed in 18 patients followed for 2-7 yrs. Recommendations for evaluation are similar to that for thunderclap headaches above

Signs

Meningismus (*see below*), hypertension, focal neurologic deficit (e.g. oculomotor palsy, hemiparesis), obtundation or coma (*see below*), ocular hemorrhage (*see below*).

Meningismus

Nuchal rigidity (especially to flexion) often ensues in 6 to 24 hrs. Patients may have a positive **Kernig sign** (flex thigh to 90° with knee bent, then straighten knee, positive sign if this causes pain in hamstrings) or **Brudzinski sign** (flex patient's neck, involuntary hip flexion is a positive sign).

Coma following SAH

Coma may follow SAH because of any one or a combination of the following[43]:

1. increased ICP
2. damage to brain tissue from intraparenchymal hemorrhage (may also contribute to increased ICP)
3. hydrocephalus
4. diffuse ischemia (may be secondary to increased ICP)
5. seizure
6. low blood flow (reduced CBF) due to reduced cardiac output (*see page 1054*)

Ocular hemorrhage

Three types of ocular hemorrhage **(OH)** may be associated with SAH. They occur alone or in various combinations in 20-40% of patients with SAH[44].

1. subhyaloid (preretinal) hemorrhage: seen funduscopically in 11-33% of cases as bright red blood near the optic disc that obscures the underlying retinal vessels. May be associated with a higher mortality rate[45]

2. (intra)retinal hemorrhage: may surround the fovea
3. hemorrhage within the vitreous humor (**Terson syndrome**). Occurs in 4-27% of cases of aneurysmal SAH[46-48], usually bilateral. May occur with other causes of increased ICP including ruptured AVMs. Funduscopy reveals vitreous opacity. Often missed on initial examination. When sought, usually present on initial exam, however it may develop as late as 12 days post SAH, and may be associated with rebleeding[47]. The mortality rate may be higher in SAH patients with vitreous hemorrhage than in those without. Patients should be followed for complications of OH (elevated intraocular pressure, retinal membrane formation → retinal detachment, retinal folds[49]). Most cases clear spontaneously in 6-12 mos. Vitrectomy should be considered in patients whose vision fails to improve[48] or if more rapid improvement is desired[50]. The long-term prognosis for vision is good in ≈ 80% of cases with or without vitrectomy[50]

The pathomechanics of OH may be due to compression of the central retinal vein and the retinochoroidal anastomoses by elevated CSF pressure[48] causing venous hypertension and disruption of retinal veins.

WORK-UP OF SUSPECTED SAH

1. tests to diagnose SAH
   A. non-contrast high-resolution CT scan: *see below*
   B. if CT is negative: LP in suspicious cases (for findings, *see below*)
2. test to identify source of SAH. Options: CTA, MRA, or digital subtraction angiography **(DSA)**. The choice needs to take into account the patient's age, renal function, and even best guess of where an aneurysm might be located
   A. MRA: no radiation, and 2D-TOF MRA (*see page 132*) does not use contrast. Poor sensitivity for aneurysm detection early after SAH (*see below*)
   B. CTA vs. angiogram: one needs to balance the risk of the procedure and ease of obtaining it against the information expected to be obtained
      1. total iodine load in a healthy adult should be < 90 gm in 24 hours. In older patients and/or possible compromised renal function, this volume should be less. CTA typically uses 65-75 cc of contrast with ≈ 300 mg iodine/ml, or ≈ 21 gm iodine. The amount of contrast with a cerebral arteriogram varies. However if an angiogram is needed after a CTA, in most cases you do not have to

wait 24 hours

2. if there is concern about renal function (e.g. serum creatinine > 100 μmol/L) hydrate the patient and optionally give Mucomyst® (*see page 124*)
3. DSA may be necessary after a positive CTA to better delineate the anatomy, or to determine dominant filling and cross flow, or in highly suspicious cases with a negative CTA (*see below*). While CTA permits reliable assessment of feasibility of endovascular treatment in most cases[51], DSA is still necessary in some

3. if CTA/angiogram is negative: see *SAH of unknown etiology*, page 1083

LABORATORY/RADIOGRAPHIC FINDINGS

CT SCAN

A good quality (e.g. no motion artifact) non-contrast high-resolution CT will detect SAH in ≥ 95% of cases if scanned within 48 hrs of SAH. Blood appears as high density (white) within subarachnoid spaces. For subtle SAH, look in the occipital horns of the lateral ventricles and the dependent portions of the sylvian fissures. CT also assesses:

1. ventricular size: hydrocephalus occurs acutely in 21% of aneurysmal ruptures[52] (also see *Hydrocephalus after SAH*, page 1044)
2. hematoma: intracerebral hemorrhage or large amount of subdural blood with mass effect may need emergent evacuation
3. infarct: not sensitive in first 24 hours after infarct (*see page 1012*)
4. amount of blood in cisterns and fissures: important prognosticator for vasospasm (*see page 1046*) and can identify pretruncal hemorrhage (*see page 1085*)
5. CT can predict aneurysm location based on the pattern of blood in ≈ 78% of cases (but mostly for MCA and A-comm aneurysms)[53]
   A. blood predominantly in anterior interhemispheric fissure (± blood in lateral ventricles) or within the gyrus rectus suggests a-comm aneurysm
   B. blood predominantly in 1 sylvian fissure is compatible with p-comm or MCA aneurysm on that side
   C. blood predominantly in the prepontine or peduncular cistern suggests a basilar apex or SCA aneurysm
   D. blood predominantly within ventricles: (also *see page 1056*)

    1. blood primarily in 4th and third ventricle: suggests lower posterior fossa source, such as PICA aneurysm or VA dissection
    2. blood primarily in the 3rd ventricle suggests a basilar apex aneurysm
6. with multiple aneurysms, CT may help identify which one bled by the location of blood (*see above*). For other "clues", *see page 1080*)

Differential diagnosis of SAH on CT

Things that can mimic the appearance of SAH on CT include:

1. pus
2. following contrast administration: sometimes IV, and especially intrathecal
3. occasionally the pachymeningeal thickening seen in spontaneous intracranial hypotension (*see page 305*)

LUMBAR PUNCTURE

The most sensitive test for SAH. However, false positives may occur, e.g. with traumatic taps (see *Differentiating SAH from traumatic tap*, page 298).

✖ Caution: lowering the CSF pressure may possibly precipitate rebleeding by increasing the transmural pressure (*see page 1044*). Therefore remove only a small amount of CSF (several ml) and use a small (≤ 20 Ga) spinal needle.

Findings (also, see *Table 14-5*, page 299):

1. opening pressure: elevated
2. appearance:
    A. non-clotting bloody fluid that does not clear with sequential tubes
    B. **xanthochromia**: yellow coloration of CSF supernatant (specimen must be centrifuged in the lab) due to heme pigments released by the breakdown of RBCs. The most reliable means of differentiating traumatic tap from SAH. Usually not apparent until 2-4 hours after the SAH. Is present in almost 100% by 12 hours after the bleed, and remains in 70% at 3 weeks, and is still detectable in 40% at 4 weeks. Spectrophotometry is more sensitive than visual inspection, but may lack sufficient specificity to warrant widespread use[54]. False positives: xanthochromia may occur with jaundice or high protein levels in the CSF
3. cell count: RBC count usually > 100,000 RBCs/mm^3. Compare RBC count in first to last tube (should not drop significantly)

4. protein: elevated due to blood breakdown products
5. glucose: normal, or reduced (RBCs may metabolize some glucose with time)

MRI

Not sensitive for SAH acutely within the first 24-48 hrs[55] (too little met-Hb) especially with thin layers of blood. Better after ≈ 4-7 days (excellent for subacute to remote SAH, > 10-20 days). FLAIR MRI is the most sensitive imaging study for detecting blood in the subarachnoid space. May be helpful in determining which of multiple aneurysms bled[56] (*see page 1080*).

Magnetic resonance angiography (MRA)

Based on a systematic review, sensitivity is 87% and specificity is 92% for detecting intracranial aneurysms **(IAs)** (compared to catheter DSA) with significantly poorer sensitivity for aneurysms < 3 mm diameter[57-59].

MRA's ability to detect IAs depends on aneurysm size, rate and direction of blood flow in the aneurysm relative to the magnetic field, and aneurysmal thrombosis and calcification. MRA may be most useful as a screening test in high-risk patients including patient's with two first degree relatives with IAs, especially those who are also smokers or hypertensive themselves[60].

CT angiography (CTA)

See *page 128*. Many centers have shown good results with CTA, with a prospective study detecting 97% of aneurysms and demonstrating CTA as safe and effective when used as the initial and sole imaging study for ruptured and unruptured cerebral aneurysms[61]. CTA shows a 3-dimensional image (as can modern catheter angiography) which can help differentiate adherent vessels from those arising from the aneurysm. CTA also demonstrates the relation to nearby bony structures which can be important in surgical planning. CTA use is increasing for evaluation of vasospasm[62].

Cerebral angiogram

The gold standard for evaluation of cerebral aneurysms. Current state of the art uses digital subtraction angiography **(DSA)**. Sometimes referred to as "catheter angiogram" to distinguish from other techniques. Demonstrates source (usually aneurysm) in ≈ 80-85% (remainder are so-called "SAH of unknown etiology", *see page 1083*). Shows if radiographic vasospasm is present (clinical

vasospasm almost never occurs < 3 days following SAH, see *Vasospasm*, page 1045) and assesses primary feeding arteries, collateral flow in case of a need for arterial sacrifice.

General principles:

1. study the vessel of highest suspicion first (in case patient's condition should change, necessitating discontinuation of procedure)
2. continue to do complete 4 vessel angiogram (even if aneurysm(s) have been demonstrated) to rule out additional aneurysms and assess collateral circulation
3. if there is an aneurysm or suspicion of one, obtain additional views to help delineate the neck and orientation of the aneurysm (*see index for specific aneurysm*)
4. ★ if no aneurysm is seen, before an arteriogram can be considered negative, must:
   A. visualize both PICA origins: 1-2% of aneurysms occur at PICA origin. Both PICAs can usually be visualized with one VA injection if there is enough flow to reflux down the contralateral VA. Occasionally it is necessary to see more of the contralateral VA than what refluxes to PICA
   B. flow contrast through the ACoA: if both ACAs fill from one side, this is usually satisfactory. It may be necessary to perform a cross compression AP study with carotid injection (first, rule-out plaque in the carotid to be compressed), or use a higher injection rate to facilitate flow through the ACoA
   C. if an infundibulum (*see below*) colocalizes to the SAH, it may be unwise to label the case as angiogram-negative[63] and exploration is recommended

Infundibulum

A funnel shaped initial segment of an artery, to be distinguished from an aneurysm. Found in 7-13% of otherwise normal arteriograms[65, 66], with a higher incidence in cases of multiple or familial aneurysms. Bilateral in 25%[66]. Most commonly found at the origin of the p-comms, but they rarely occur at other sites. Criteria (somewhat arbitrary) for differentiating infindibula from aneurysms are shown in *Table 30-1*. Infundibula may represent incomplete remnants of previous fetal vessels[67 (p 272)]

Although they may bleed[63, 68-70], there is less risk of rupture than with a saccular aneurysm (no infundibulum < 3 mm in size bled[71] in the cooperative study). However, infundibula have been documented to progress to an aneurysm which may bleed (13 case reports in the literature as of 2009). Recommended treatment: at the time of surgery for another reason, consider treating an infundibulum with wrapping, or placing in an encircling clip, or sacrificing the artery if it can be done safely (infundibula lack a true neck).

Table 30-1 Criteria of an infundibulum

1. triangular in shape
2. mouth (widest portion) < 3 mm[64]
3. vessel at apex

Angiographic findings

1. general features to take note of when analyzing an aneurysm on angiogram (special considerations for specific aneurysms are covered in designated sections)
   A. size of aneurysm dome:
      1. MRI or CT helps with this since the aneurysm may be partially thrombosed and the filling part may be much smaller than the overall size
      2. large aneurysms (≥ 15 mm dia.) are associated with lower rates of complete occlusion by endovascular coiling[72, 73]
   B. neck size
      1. narrow necks < 5 mm are ideal for coiling[74]
      2. broad necks ≥ 5 mm are associated with increased risk of incomplete occlusion and recanalization with coiling[73]
      3. stent or balloon-assisted coiling may be needed for wide necked aneurysms. Stents should be avoided if possible *see page 1060*
   C. dome:neck ratio ≥ 2 is associated with higher rate of coil occlusion[74]
2. basilar bifurcation aneurysms: *see page 1074*

30.2. Grading SAH

Two widely quoted grading scales are presented here.

HUNT AND HESS GRADE

See *Table 30-2* and *Table 30-3* for grading system. Grades 1 and 2 were operated upon as soon as an aneurysm was diagnosed. Grade ≥ 3 managed until the condition improved to Grade 2 or 1. Exception: life threatening hematoma or multiple bleeds (which were operated on regardless of grade).

Analysis of data from the International Cooperative Aneurysm Study revealed that with normal consciousness, Hunt and Hess **(H&H)** grades 1 and 2 had identical outcome, and that hemiparesis and/or aphasia had no effect on mortality.

Mortality:

Admission Hunt and Hess Grade 1 or 2: 20%.
Patients taken to O.R. (for any procedure) at H&H Grade 1 or 2: 14%.
Major cause of death in Grade 1 or 2 is rebleed.
Signs of meningeal irritation increases surgical risk.

A. also appears in the literature as World Federation of Neurological Surgeons

WORLD FEDERATION OF NEUROSURGICAL SOCIETIES[A] (WFNS) GRADING OF SAH

The WFNS Committee on a Universal SAH Grading Scale[77, 78] grading system is shown in *Table 30-4*. It uses the Glasgow Coma Scale **(GCS)** (see *Table 12-1*, page 279) to evaluate level of consciousness, and uses the presence or absence of major focal neurologic deficit to distinguish grade 2 from grade 3.

Table 30-2 Hunt and Hess classification* of SAH[75]

Grade	Description
1	asymptomatic, or mild H/A and slight nuchal rigidity
2	Cr. N. palsy (e.g. III, VI), moderate to severe H/A, nuchal rigidity
3	mild focal deficit, lethargy, or confusion
4	stupor, moderate to severe hemiparesis, early decerebrate rigidity
5	deep coma, decerebrate rigidity, moribund appearance

Add one grade for serious systemic disease (e.g. HTN, DM, severe athero-sclerosis, COPD) or severe

vasospasm on arteriography.

* original paper did not consider patient's age, site of aneurysm, or time since bleed; patients were graded on admission and pre-op

Table 30-3 Modified classification[76] adds the following

Grade	Description
0	unruptured aneurysm
1 a	no acute meningeal/brain reaction, but with fixed neuro deficit

Table 30-4 WFNS SAH grade[77]

WFNS grade	GCS score*	Major focal deficit†
0‡		
1	15	–
2	13-14	–
3	13-14	+
4	7-12	+ or –
5	3-6	+ or –

* GCS = Glasgow Coma Scale, see Table 12-1, page 279

† aphasia, hemiparesis or hemiplegia (+ = present, – = absent)

‡ intact aneurysm

30.3. Initial management of SAH

Initial management concerns

1. rebleeding: the major concern during the initial stabilization
2. hydrocephalus: precipitous development acute hydrocephalus may be obstructive (due to blockage of CSF flow by blood clot), but presence of ventriculomegaly early after SAH as well as at later stages is often due to communicating hydrocephalus (due toxic effect of blood breakdown products on arachnoid granulations) (see *Hydrocephalus after SAH*, page 1044)
3. delayed ischemic neurologic deficit **(DIND)**, usually attributed to vasospasm. Begins to be of concern several days following the SAH

4. hyponatremia with hypovolemia: *see page 1043*
5. DVT and pulmonary embolism: *see page 42*
6. seizures: *see page 1041*
7. determining source of bleeding: should be investigated early with CTA or catheter angiography. The timing and choice of study takes into consideration the patient's condition (unstable or pre-morbid patients are not candidates), the feasibility of early treatment (ideal), and the likelihood of endovascular therapy (based on patient's age and predicted aneurysm location as well as availability)

Goals of medical management related to neurologic injury

In addition to prevention of hyponatremia, hypovolemia, seizures, etc. (*see above*), the goals of initial medical management include:

1. augmenting CBF: the main device for accomplishing this is hyperdynamic therapy (*see page 1052*). Goals are:
   A. increasing cerebral perfusion pressure **(CPP)**
   B. improving blood rheology: RBC aggregability increases after SAH[79]
   C. maintaining euvolemia: the majority of patients become hypovolemic in the first 24 hrs after SAH. Also, avoid prophylactic *hyper* volemia
   D. maintaining normal ICP
2. neuroprotection: there are currently no medications shown to be effective or approved for use as neuroprotective agents for this or any other type of brain injury. Animal studies have shown time and again that the concept may someday be translated into clinical practice[80]

30.3.1. Monitors/tubes

Also see *Admitting orders* below.

1. arterial-line: for patients who are hemodynamically unstable, stuporous or comatose, those with difficult to control hypertension, or those requiring frequent labs (e.g. ventilator patients)
2. intubate patients who are comatose or unable to protect airway (e.g. stridorous)
3. pulmonary-artery catheter (PA-catheter, AKA Swann-Ganz catheter): the safety and efficacy of this device has been debated in the critical care

literature for over a decade now, with some calling for a moratorium on PA catheter use[81]. It is possible that newer technologies may supplant the need for this invasive procedure while allowing close hemodynamic monitoring[82]. Nevertheless, a PA catheter can be considered for:

   A. Hunt and Hess **(H&H)** grade ≥ 3 (except good grade 3 patients)
   B. patients with possible CSW or SIADH
   C. hemodynamically unstable patients

4. cardiac rhythm monitor: arrhythmias may occur following SAH (*see page 1054*)
5. **intraventricular catheter (IVC)** AKA ventriculostomy. Possible indications:
   A. patients developing acute hydrocephalus following SAH or in those with significant intraventricular blood (allows measurement of ICP as well as drainage of blood laden CSF). IVC causes symptomatic improvement in almost two-thirds[52]. May increase the risk of rebleeding (*see page 1044*), however, the risk of untreated hydrocephalus is probably higher[83]
   B. H&H grade ≥ 3 (except good grade 3 patients). If a high grade patient improves with an IVC, the prognosis may be more favorable. If ICP is elevated, management includes the use of mannitol (see *Treatment measures for elevated ICP*, page 876)

30.3.2. Admitting orders

1. admit to ICU (monitored bed)
2. VS with neuro checks q 1 hr
3. activity: BR with HOB at 30°. SAH precautions (i.e. low level of external stimulation, restricted visitation, no loud noises)
4. nursing
   A. strict I's & O's
   B. daily weights
   C. knee high TED hose and pneumatic compression boots **(PCB)**
   D. indwelling Foley catheter if patient lethargic, incontinent, or unable to void in urinal or bedpan. Consider temperature sensing catheter for strict fever control
5. diet: NPO (in preparation for surgery or endovascular intervention)

6. IV fluids: early aggressive fluid therapy to head off cerebral salt wasting
   A. NS + 20 mEq KCl/L at ≈ 2 ml/kg/hr (typically 140-150 ml/hr) (see *Blood pressure and volume management* below)
   B. if Hct < 40%[84], give 500 ml of 5% albumin over 4 hrs upon admission
7. medications (avoid IM medications to reduce pain)
   A. prophylactic anticonvulsants
      1. seizure incidence: excluding seizures at the time of hemorrhage, ≈ 3% of patients with SAH have seizures during the acute illness[85]. 5% have a seizure in the immediate post-op period with or without SAH[86]. 10.5% incidence in 5 years follow-up (20% for MCA, 9% for PCA, and 2.5% for ACA aneurysms)[87]
      2. use of prophylactic anticonvulsants is controversial[88], however, a generalized seizure may be devastating in the presence of a tenuous aneurysm, and thus AEDs are given by many authorities[89] at least for 1 week post-op[86]
      3. Keppra® (levetiracetam): start with 500 mg PO or IV q 12 hours
      4. if levetiracetam not available: phenytoin may be used. Avoid IV if possible because of pain and phlebosclerosis (circumvented with fosphenytoin). Load with 17 mg/kg, maintenance of 100 mg TID
      5. some prophylaxis is provided by barbiturates (e.g. phenobarbital) when given for sedation (*see below*) or burst suppression in the O.R.
   B. sedation (not oversedation): e.g. with propofol
   C. analgesics: fentanyl (unlike morphine, does not cause histamine release. Lowers ICP) 25-100 mcg (0.5-2 ml) IVP, q 1-2 hrs PRN (avoid Demerol® because it may lower seizure threshold)
   D. dexamethasone (Decadron®): may help with H/A and neck pain. Effect on edema controversial. Usually given pre-op prior to craniotomy
   E. stool softener in patients able to take PO (docussate 100 mg PO BID)
   F. anti-emetics: avoid phenothiazines which may lower seizure threshold. Use e.g. Zofran® (ondansetron) 4 mg IV over 2-5 minutes, may repeat in 4 & 8 hours, and then q 8 hours for 1-2 days
   G. calcium channel blockers (see *Calcium channel blockers*, page 1053): nimodipine (Nimotop®) 60 mg PO/NG q 4 hrs initiated within 96 hrs of SAH (some use 30 mg q 2 hrs to avoid periodic dips in BP). IV administration is equally as effective[90] where available

H. H_2 blockers (e.g. ranitidine) or proton pump inhibitors (e.g. Prevacid® (lansoprazole) 30 mg p.o. or IV q d): to reduce risk of stress ulceration

I. ✖ these agents impair coagulation and are used with caution: ASA, dextran[91], heparin, and repeated administration of hetastarch (Hespan®)[92, 93] over a period of days

8. oxygenation
   A. in non-intubated patient: O_2 2 L per NC PRN (based on ABG) if tolerated
   B. in ventilated patient: strive for normocarbia and pO_2 > 100 mm Hg
9. HTN: SBP 120-150 mm Hg by cuff is a guideline with unclipped aneurysm (see *Blood pressure and volume management* below)
10. labs
    A. ABG, electrolytes, CBC, PT/PTT on admission
    B. ABG, electrolytes, CBC q day (ABG q 6 hrs if patient unstable, electrolytes q 12 hrs if hyponatremia develops, see *Hyponatremia following SAH* below)
    C. serum and urine osmolality if urine output high or low (see *Syndrome of inappropriate antidiuretic hormone secretion (SIADH)*, page 10)
    D. follow Hct and (optional) serum fibrinogen (to assess viscosity, important for blood flow in vasospasm)
    E. CXR daily until stable: patients undergoing triple-H therapy can develop dangerous pulmonary edema as they “fall off” the Starling curve with volume expansion. Patients with SAH are also rarely at risk for neurogenic pulmonary edema[94], *see page 28*
    F. if available, transcranial doppler to monitor MCA, ACA, ICA, VA and BA velocities and Lindegaard ratio (*see page 1048*) q Mon, Weds & Fri

30.3.3. Blood pressure and volume management

With an unsecured (unclipped or uncoiled) aneurysm, gentle volume expansion with slight hemodilution and mild elevation of blood pressure may help prevent or minimize the effects of vasospasm[95] and cerebral salt wasting. However, extreme hypertension must be avoided (to reduce risk of rebleeding). Hypervolemia is to avoided since it does not mitigate vasospasm and increases complications[96].

With a secured aneurysm, aggressive volume expansion with hyperdynamic therapy is commonly used (*see page 1052*).

Initial blood pressure

Ideal blood pressure is controversial, and must take patient's baseline into consideration, **SBP ≈ 120-150** by cuff is a guideline.

If blood pressure is labile, labetalol or nicardipine should be used in conjunction with an arterial-line. Avoid hypotension as it may exacerbate ischemia.

Long acting drugs (e.g. ACE inhibitors such as Vasotec (*see page 20* for IV, or *page 21* for PO)) should be started in patients requiring continued therapy. In patients who were normotensive prior to SAH with easily controlled hypertension, Vasotec may be used PRN in conjunction with a beta blocker (e.g. labetalol, *see page 21*).

30.3.4. Hyponatremia following SAH

Background

Hypovolemia and hyponatremia frequently follow SAH as a result of natriuresis and diuresis. Although hyponatremia had been attributed to a rise in ADH[97] (thought to produce SIADH with *hyper* volemia), the ADH increment is usually transient, lasting only ≈ 4 days and hypervolemia did not occur. Another theory is based on the fact that there is often a delayed peak in **atrial natriuretic factor (ANF)** (a 28-amino acid polypeptide) after an initial smaller rise[98] that was frequently followed by urinary loss of sodium (**cerebral salt wasting (CSW)**, *see page 13*) that mimics SIADH, and volume depletion. Although CSW has clearly been shown to be the cause of hyponatremia in the majority of these patients[99], there are still doubts that ANF is *the* operative natriuretic factor in SAH[100]. A rise in ANP and brain natriuretic peptide **(BNP)** after SAH is associated with the development of a negative fluid balance[101].

Routine labs are identical in SIADH and CSW[102], but the extracellular fluid volume (which is more difficult to measure) is low in CSW and is normal or elevated in SIADH (see *Table 2-5*, page 14 for a comparison of the two conditions). The neurologic effects of hyponatremia (*see page 9*) may mimic delayed ischemic neurologic deficit from vasospasm, and hyponatremic patients have about 3 times the incidence of delayed cerebral infarction after SAH than

normonatremic patients[103].

Factors that may increase the risk of hyponatremia after SAH include: history of diabetes, CHF, cirrhosis, adrenal insufficiency, or the use of any of the following drugs: NSAIDs, acetaminophen, narcotics, thiazide diuretics[104].

Treatment

✖ Caution! Restricting fluids which is the treatment for SIADH may be hazardous in the case of CSW (which is more likely to occur after SAH than is SIADH) since dehydration increases blood viscosity which exacerbates ischemia from vasospasm[103].

- treat hypovolemia with infusions of crystalloid (e.g. NS), PRBCs, or colloids (avoid repeated administration of hetastarch, *see above*)
- treat the hyponatremia of CSW as outlined on *see page 14*. NB: too rapid correction or over-correction carries the risk of osmotic myelinolysis, *see page 11*

30.3.5. Rebleeding

Approximately 3000 North Americans die each year from rebleeding of ruptured cerebral aneurysms[115]. For untreated ruptured aneurysms, the maximal frequency of rebleeding is in the 1st day (4% on day 1), then 1.5% daily for 13 d. 15-20% rebleed within 14 d, 50% will rebleed within 6 months, thereafter the risk is ≈ 3%/yr[A] with a mortality rate of 2%/yr[116]. 50% of deaths occur in the 1st month. In a study of 33 patients who rebled, the highest risk of rebleeding occurred in the first 6 hours following SAH[117].

A. to understand the calculation of cumulative risk for aneurysmal rupture, *see page 1100* (that discussion is related to AVMs but the same concepts pertain to aneurysms)

The rebleeding risk increases in patients with higher Hunt and Hess grades[117].

Pre-operative ventriculostomy (e.g. for acute post-SAH hydrocephalus) (*see page 1044*) and possibly lumbar spinal drainage (*see page 1062*) increase the risk of rebleeding.

The risk of rebleeding in SAH of unknown etiology and with AVMs, as well as the risk of bleeding with incidental multiple unruptured aneurysms, are all similar at ≈ 1%/yr (may actually be less in SAH of unknown etiology, *see page 1083*)[118].

Prevention of rebleeding

The *optimal* method of preventing rebleeding is early coiling or surgical clipping. Bed rest and hyperdynamic therapy do not prevent rebleeding[89].

Antifibrinolytic therapy: The role of clot lysis in early rebleeding is uncertain.

tranexamic acid (Cyklokapron®) DRUG INFO

Reduces the risk of early rebleeding[119].

Rx: 1 gm IV as soon as diagnosis of SAH is verified (if patient is to be transported to another facility for definitive care, the dose is given before transport), followed by 1 gm q 6 hours until the aneurysm is occluded; this treatment did not exceed 72 hours.

✖ epsilon-aminocaproic acid (Amicar®) DRUG INFO

(EACA) an antifibrinolytic agent, competitively inhibits activation of plasminogen to plasmin. Existing plasmin is neutralized by endogenous antiplasmins. EACA does reduce the risk of rebleeding. However, the incidence of hydrocephalus and delayed ischemic deficits (vasospasm) are increased[120] with prolonged use. There may also be a lag of 24-48 hrs before effectiveness occurs[121]. Because of the increased rate of cerebral infarction, EACA was found not to reduce early mortality, and its use was discouraged.

Reevaluation in a non-randomized study[122] excluding grade IV and V patients, suggests that the problems with EACA may be minimized by use of an IV loading dose (to eliminate the lag-period to effectiveness) and by limiting the length of time of use to that time until the patient can undergo early surgery. Further study is needed.

Rx high-dose[122]: EACA 10 gm IV loading dose, followed by 48 gm/day continuous maintenance infusion. Maintenance dose is adjusted to serum EACA levels.

30.3.6. Hydrocephalus after SAH

For hydrocephalus after traumatic SAH, *see page 906*.

ACUTE HYDROCEPHALUS

The frequency of hydrocephalus **(HCP)** on the initial CT after SAH depends on the defining criteria used, with a reported range of 9-67%[123]. A realistic range is ≈15-20% of SAH patients, with 30-60% of these showing no impairment of consciousness[123, 124]. 3% of those without HCP on initial CT develop HCP within 1 week[123].

Factors felt to contribute to acute HCP include: blood interfering with CSF flow through the Sylvian aqueduct, fourth ventricle outlet, or subarachnoid space, and/or with reabsorption at the arachnoid granulations.

Findings associated with acute HCP include[124]:

- increasing age
- admission CT findings: intraventricular blood, diffuse subarachnoid blood, and thick focal accumulation of subarachnoid blood (intraparenchymal blood did not correlate with chronic HCP, and patients with a normal CT had a low incidence)
- hypertension: on admission, prior to admission (by history), or post-op
- by location:
  - posterior circulation aneurysms have a higher incidence of HCP
  - MCA aneurysms correlate with low incidence of HCP
- miscellaneous: hyponatremia, patients who were not alert on admission, use of preoperative antifibrinolytic agents, and low Glasgow outcome score

Treatment

About half the patients with acute HCP and impaired consciousness improved spontaneously[123]. Patients in poor grade (H&H IV-V) with large ventricles may be symptomatic from the HCP and consideration should be given to ventriculostomy which caused improvement in ≈ 80% of patients in whom it was used[123]. There is probably an increased risk of aneurysmal rebleeding in patients undergoing ventriculostomy shortly after SAH[123, 125, 126] especially if performed early and if ICP is lowered precipitously. The mechanism is controversial, but may be due to an increase in the **transmural pressure** (the pressure across the aneurysm wall which equals the difference between arterial

pressure and ICP).

When a ventriculostomy is used, it is recommended to keep ICP in the range of **15-25 mm Hg**[127] and to avoid rapid pressure reduction (unless absolutely necessary) to decrease the risk of IVC induced aneurysmal rebleeding.

Chronic HCP

Chronic HCP is due to piaarachnoid adhesions or permanent impairment of the arachnoid granulations. Acute HCP does not inevitably lead to chronic HCP. 8-45% (reported range in literature[128]) of all ruptured aneurysm patients, and ≈ 50% of those with acute HCP following SAH need permanent CSF diversion. The presence of intraventricular blood increases this risk[128]. There is controversy as to whether the use of ventriculostomy for acute HCP increases[129] or possibly even decreases[128] the incidence of shunt dependency.

30.4. Vasospasm

Key concepts:

- delayed cerebral ischemic symptoms and/or cerebral arterial narrowing on angiography that follows some cases of SAH (usually), trauma, or other insults
- time course: almost never before day 3 post SAH, peak incidence 6-8 days post SAH, rarely starts after day 17. Main time of risk: 3-14 days post SAH
- risk factors: higher SAH grade, more blood on CT
- results in pathologic changes within the vessel walls (not just vasoconstriction)
- diagnosis: may be clinical, angiographic, or with transcranial Doppler
- treatment: none are curative. Mainstays: “triple H” therapy (hypertension, hypervolemia, hemodilution), direct vasodilatation (angioplasty or intraarterial verapamil), and possibly routine use of statins following SAH

Cerebral vasospasm is a condition that is most commonly seen following aneurysmal subarachnoid hemorrhage **(SAH)**, but may also follow other intracranial hemorrhages (e.g. intraventricular hemorrhage from AVM[130], and SAH of unknown etiology), head trauma (with or without SAH)[131], brain surgery, lumbar puncture, hypothalamic injury, infection, and may be associated

with preeclampsia (*see* *page 73*). Vasospasm has two not-necessarily reconcilable definitions (see *Definitions* below):

1. clinical vasospasm: *see below*
2. radiographic vasospasm: *see below*

30.4.1. Definitions

CLINICAL VASOSPASM

AKA **delayed ischemic neurologic deficit (DIND)**, AKA symptomatic vasospasm. A delayed ischemic neurologic deficit following SAH. Clinically characterized by confusion or decreased level of consciousness sometimes with focal neurologic deficit (speech or motor). The diagnosis is one of exclusion, and sometimes cannot be made with certainty.

For clinical findings, *see page 1045*.

RADIOGRAPHIC VASOSPASM (AKA ANGIOGRAPHIC VASOSPASM)

Arterial narrowing demonstrated on cerebral angiography, often with slowing of contrast filling. The diagnosis is solidified by previous or subsequent angiograms showing the same vessel(s) with normal caliber. Since only larger arteries may be visualized angiographically, the diagnosis is limited to narrowing of these vessels. In some cases a DIND corresponds to a region of vasospasm seen angiographically.

30.4.2. Characteristics of cerebral vasospasm

Clinical findings

Findings usually develop gradually, and may progress or fluctuate. May include:

1. non-localizing findings
   A. new or increasing H/A
   B. alterations in level of consciousness (lethargy…)
   C. disorientation
   D. meningismus
2. focal neurological signs may occur including cranial nerve palsies and focal motor deficits. Also, symptoms may cluster into one of the following “syndromes” (vasospasm incidence is higher in the distribution of the

ACA than in that of the MCA)

A. **anterior cerebral artery (ACA) syndrome**: frontal lobe findings predominate (abulia, grasp/suck reflex, urinary incontinence, drowsiness, slowness, delayed responses, confusion, whispering). Bilateral anterior cerebral artery distribution infarcts are usually due to vasospasm following an ACoA aneurysm rupture
B. **middle cerebral artery (MCA) syndrome**: hemiparesis, monoparesis, aphasia (or apractagnosia of non-dominant hemisphere - inability to use objects or perform skilled motor activities, due to lesions in the lower occipital or parietal lobes; subtypes: ideomotor apraxia and sensory apraxia)

Incidence

- radiographic cerebral vasospasm **(CVS)** is identified in 30-70% of arteriograms performed around the 7th day following SAH, whereas DIND associated with radiographic CVS occurs in only 20-30% of patients with SAH[22]
- radiographic CVS may occur in the absence of clinical deficit, and vice-versa

Severity

- CVS is the most significant cause of morbidity and mortality in patients surviving SAH long enough to reach medical care, even exceeding direct effects of aneurysmal rupture as well as rebleeding
- CVS ranges in severity from mild reversible dysfunction, to severe permanent deficits secondary to ischemic infarction in 7% of SAH patients, extensive enough to be fatal in 7% of SAHs[22]
- earlier onset of CVS is associated with greater deficit

Time course of vasospasm

- onset: almost never before day 3 post-SAH[132]
- maximal frequency of onset during days 6-8 post-SAH (however, rarely can occur as late as day 17). Typical atrisk period is quoted as **days 3-14**
- clinical CVS is almost always resolved by day 12 post-SAH. Once radiographic CVS is demonstrated, it usually resolves slowly over 3-4 weeks

- onset is usually insidious, but ≈ 10% have an abrupt and severe deterioration

Correlated findings

- blood clots are especially spasmogenic when in direct contact with the proximal 9 cm of the ACA and the MCA
- not all patients with SAH develop CVS, and CVS can follow other insults besides SAH (e.g head trauma without SAH)
- the Hunt and Hess grade on admission correlates with the risk of CVS (*see Table 30-5*)
- the amount of blood on CT correlates with the severity of CVS[133, 134] (*see Table 30-6*) (also holds true for traumatic SAH[3])
- higher incidence with increasing age of patient
- a history of active cigarette smoking is an independent risk factor[135]
- history of preexisting hypertension
- there is good but not perfect correlation between the site of major blood clots on CT, the focality of delayed ischemic neurological deficits, and the visualization of angiographic CVS in corresponding arteries
- pial enhancement on CT ≈ 3 days after SAH (with IV contrast administration) may correlate with higher risk of CVS (indicates increased permeability of BBB)[136], but this is controversial[137]
- for patients undergoing early surgery, if there is little SAH left on a CT done 24 hours post-op, there is little risk of vasospasm
- antifibrinolytic therapy reduces rebleeding, but increases the risk of hydrocephalus and vasospasm[120] (*see page 1043*)
- angiographic dye can exacerbate CVS
- hypovolemia

Table 30-5 Correlation of DIND with Hunt and Hess grade

Hunt and Hess grade	% DIND (clinical vasospasm)
1	22%
2	33%
3	52%
4	53%
5	74%

Table 30-6 Grading system of Fisher[133]
(correlation between the amount of blood on CT and the risk of vasospasm)

Fisher group	Blood on CT*	No. of pts.	-- VASOSPASM --		
			Angiographic		Clinical vasospasm (DIND)
			Slight	Severe	
1	no subarachnoid blood detected	11	2	2†	0
2	diffuse or vertical layers‡ < 1 mm thick	7	3	0	0
3	localized clot and/or vertical layer‡ ≥ 1 mm	24	1	23	23
4	intracerebral or intraventricular clot with diffuse or no SAH§	5	2	0	0

* measurements made in the greatest longitudinal & transverse dimension on a printed EMI CT scan (no scaling to actual thickness) performed within 5 d of SAH in 47 patients; falx never contributed more than 1 mm thickness to interhemispheric blood

† may actually be 0 since 1 patient was scanned late and 1 developed spasm only peripherally

‡ "vertical layer" refers to blood within "vertical" subarachnoid spaces including interhemispheric fissure, insular cistern, ambient cistern

§ reflux of blood into ventricles frequently indicates obstruction of CSF circulation, and is associated with high incidence of hydrocephalus

30.4.3. Pathogenesis

Poorly understood. Risk of developing vasospasm is higher in cases where arterial blood at high pressure contacts the vessels at the base of the brain. Rarely occurs in the setting of intraparenchymal or intraventricular hemorrhage (e.g. from AVM) or in SAH with distribution limited to the cerebral convexity.

Pathological changes observed within the vessel wall are outlined in *Table 30-7*.

Table 30-7 Pathological changes in vasospasm

Time	Vessel layer	Pathologic change
day 1-8	adventitia	↑ inflammatory cells (lymphocytes, plasma cells, mast cells) and connective tissue
	media	muscle necrosis and corrugation of elastica
	intima	thickening with endothelial swelling and vacuolization, opening of interendothelial tight junctions[138, 139]
day 9-60	intima	proliferation of smooth muscle cells → progressive intimal thickening

In humans, CVS is a chronic condition with definite long-term changes in the morphology of the involved vessels. Endothelin 1 (ET1) appears to be a critical mediator and has been shown to cause potent and prolonged vasospasm[140].

30.4.4. Diagnosis of cerebral vasospasm

Diagnosis requires appropriate clinical criteria, and ruling-out other conditions that can produce delayed neurologic deterioration, as shown in *Table 30-8*.

Table 30-8 Diagnosis of clinical vasospasm[141]

- delayed onset or persisting neuro deficit
- onset 4-20 days post-SAH
- deficit appropriate to involved arteries
- rule-out other causes of deterioration
  - rebleeding
  - hydrocephalus
  - cerebral edema
  - seizure
  - metabolic disturbances: hyponatremia…
  - hypoxia
  - sepsis
- ancillary tests (*see text*)
  - transcranial Doppler
  - CBF studies
  - SPECT
  - cerebral angiography

Ancillary tests for vasospasm

In addition to angiographically demonstrating vasospasm:

- transcranial doppler **(TCD)**: *see below*
- alterations in intracranial pulse wave[142]
- CTA: can demonstrate vasospasm[143]
- MRA: may be useful for management of vasospasm (not a practical alternative to conventional angiography)[144]
- continuous quantitatively analyzed EEG monitoring in the ICU:
  - a decline of the percent of alpha activity (defined here as 6-14 Hz) called "relative alpha" **(RA)** from a mean of 0.45 to 0.17 predicted the onset of vasospasm earlier than TCD or angiographic changes[145]
  - a decline of total EEG power (amplitude) was 91% sensitive for predicting vasospasm[146]
- alterations in cerebral blood flow **(CBF)**:

- ★ MRI: DWI and PWI may detect early ischemia (*see page 132*)
- ★ CT perfusion study (*see page 128*)
- ◆ xenon CT: may detect large global changes in CBF, but too insensitive to detect focal blood flow changes[147, 148]
- ◆ positron emission tomography **(PET)**[149] or SPECT scans (nonquantitative, and takes longer than xenon studies)

Transcranial doppler (TCD)

Noninvasive method of semiquantitatively measuring velocity of blood flow in a specific artery through the skull (in regions of thinner bone - insonation windows) utilizing ultrasound phase shift.

Narrowing of the arterial lumen as occurs in vasospasm elevates the blood flow velocity which may be detected with TCD[150-152]. Detectable changes may precede clinical symptoms by up to 24-48 hrs. Findings are often more helpful when baseline studies performed before vasospasm is likely to have begun are available.

Typical values are shown for the MCA in *Table 30-9*. Also, daily increases of > 50 cm/sec may suggest vasospasm. There is less correlation between velocities and vasospasm in the anterior cerebral arteries (ACA). Distinguishing vasospasm from hyperemia (which increases blood flow velocities in both the MCA and the ICA) is facilitated by using the ratio of these velocities (the so-called **Lindegaard ratio**) also shown in *Table 30-9*.

Once values become elevated, it often takes several weeks to go back down.

Table 30-9 Interpretation of transcranial doppler for vasospasm

Mean MCA velocity (cm/sec)	MCA:ICA (Lindegaard) ratio	Interpretation
< 120	< 3	normal
120-200*	3-6	mild vasospasm*
> 200	> 6	severe vasospasm

* velocities in this range are specific for vasospasm but are only ≈ 60% sensitive

30.4.5. Treatment for vasospasm

See *page 1050* for management protocol.

Numerous treatments for cerebral arterial vasospasm have been evaluated.

See the survey articles by Wilkins[153, 154] for an extensive list of agents and techniques studied. Vasospasm in humans does not respond to the large variety of drugs that reverse experimental vasospasm in animal models.

Prevention of vasospasm

Vasospasm can often be mitigated by preventing post-SAH hypovolemia and anemia by employing hydration and blood transfusion. Although early aneurysm treatment (clipping or coiling) does not prevent CVS (in fact, manipulation of vessels may increase the risk), it facilitates treatment of CVS by eliminating the risk of rebleeding (permitting safe use of hyperdynamic therapy) and removal of clot (*see below*) may reduce the incidence of CVS (see *Timing of aneurysm surgery*, page 1060 for discussion of early surgery). Routine use of statins shows promise for reducing effects of vasospasm (*see below*). ✖ Prophylactic (i.e. before vasospasm has been diagnosed) hyperdynamic therapy (triple H therapy - *see page 1052*) is not indicated (it may cause complications and does not provide any benefit)[96].

Vasospasm treatment options

Treatment options fall into the following categories:

1. direct pharmacological arterial dilatation
   A. smooth muscle relaxants:
      1. calcium channel blockers*: did not succeed in counteracting vasospasm, but they may provide a neuroprotectant effect (*see page 1053*)
      2. endothelin receptor antagonists†: ET_A antagonists (clazosentan) and $ET_{A/B}$ antagonists[155, 156]
   B. sympatholytics
   C. intraarterial papaverine§[157,158]: short-lived (*see below*)
   D. αICAM-1 inhibition† (antibody to intracellular adhesion molecule)
2. direct mechanical arterial dilatation: balloon angioplasty§ (*see below*)
3. indirect arterial dilatation: utilizing hyperdynamic therapy* (*see below*)
4. surgical treatment to dilate arteries: cervical sympathectomy‡[159]
5. removal of potential vasospasmogenic agents
   A. removal of blood clot: does not completely prevent vasospasm
      1. mechanical removal at the time of aneurysm surgery[160, 161]
      2. subarachnoid irrigation with thrombolytic agents† at the time of

surgery or post-op through cisternal catheters[162-165] (must be initiated within ≈ 48 hrs of clipping) or intrathecally[166]. Hazardous with incompletely clipped aneurysm[165]

B. CSF drainage: via serial lumbar punctures, continuous ventricular drainage, or postoperative cisternal drainage[167]

6. protection of the CNS from ischemic injury:
   A. calcium channel blockers* (*see page 1053*)
   B. NMDA (N-methyl-D-aspartate) receptor antagonists†
      1. Selfotel®: a selective competitive NMDA receptor antagonist (like PCP & ketamine), and like these agents, may cause hallucinations, paranoia, delerium… at all but the lowest doses[168]. Recently abandoned in studies for use in acute stroke due to an increase in brain-related deaths[169]. No benefit demonstrated in severe closed head injury[170]
      2. eliprodil
      3. cerestat
   C. free radical scavengers†
      1. tirilazad mesylate (Freedox®): a 21-aminosteroid. Improved outcome was observed in males given 6 mg/kg/d[171] (females metabolize the drug at 3-4 **x** the rate as males, and a study with 15 μg/kg/d in females is planned). Overall the drug does not look as promising as it did initially
      2. nicaraven[172]
7. improvement of the rheologic properties of intravascular blood to enhance perfusion of ischemic zones (also an endpoint of hyperdynamic therapy)* (*see page 1052*)
   - includes: plasma, albumin, low molecular weight dextran‡, perfluorocarbons†, mannitol (*see page 1063*)
   - the optimal hematocrit is controversial, but ≈ 30-35% is a good compromise between lowered viscosity without overly reducing O_2 carrying capacity (hemodilution is used to lower Hct; phlebotomy is not used)
8. other pharmacologic agents: statins
9. extracranial-intracranial bypass around zone of vasospasm‡[173,174]

* technique that is generally accepted for standard usage

§ technique that is accepted for use but not necessarily standard or available at all centers

† experimental or research technique with potential for future application

‡ technique not generally used or no longer accepted

Promising agents in trials

- **nicardipine prolonged release implants (NPRIs)**: placed intra-op in the cisterns (where thick clots were located) decreased the incidence of vasospasm in patients with thick blood clots (Fisher Group 3, see *Table 30-6*, page 1046)[175]
- **clazosentan** (AXV-034343): a selective endothelin IA receptor antagonist[176]: reduces frequency and severity of vasospasm
- **statins**: meta-analysis[177] of 3 small studies showed a reduction in radiographic vasospasm, DIND, and mortality with the use of statins. This suggests that routine use of statins after SAH by be warranted. Agents reported:
  A. simvastatin 80 mg/d[178, 179]
  B. pravastatin 40 mg/d[180]

Vasodilatation by angioplasty

Catheter directed balloon angioplasty of vessels demonstrated to be in vasospasm[181, 182]: available only in centers with interventional neuroradiologists. Risks of the procedure: arterial occlusion, arterial rupture, displacement of aneurysm clip[183, 184], arterial dissection. Only feasible in large cerebral vessels (distal arteries not accessible). Clinical improvement occurs in ≈ 60-80%.

Criteria for transluminal balloon angioplasty **(TBA)**:

1. failure of hyperdynamic therapy
2. ruptured aneurysm is repaired
3. optimal results when performed within 12 hours of onset of symptoms
4. may be done immediately post-clipping for vasospasm that was observed pre-op
5. controversial: asymptomatic vasospasm seen on the contralateral side during angioplasty for ipsilateral vasospasm. Some would balloon the asymptomatic side, but others cite the complication rate and would observe
6. ✖ cerebral infarction (CVA): a contraindication to TBA

Vasodilatation by intraarterial drug injection

Vasodilatation by intraarterial drug **(IAD)** injection may be considered the "poor-man's" angioplasty since it could be performed by angiographers who are not interventional neuroradiologists. However, the effects are shorter-lived and less profound at their peak than with angioplasty. While IAD can be repeated, this requires multiple arterial catheterizations. IAD is still of value to help open up vessels to allow placement of the angioplasty balloon, and for vessels inaccessible to angioplasty balloons.

Agents used for vasodilatation:

1. papaverine: usually 200-300 mg infused over 30 mins. May exacerbate vasospasm in some cases[185], may produce thrombocytopenia[186], and unless carefully titrated, it can elevate ICP[187]. Largely abandoned because of limited success
2. verapamil: angiography of ICA is performed. If vasospasm is seen, 8 mg of vera-pamil is injected over 2 minutes (***Rx***: mix 2 vials of Verapamil (each vial is 5 mg in 2 cc) with 6 cc of NS to get 10 mg in 10 cc, inject 8 cc to give 8 mg). Then the other ICA is checked, and similarly injected if indicated. Can also be done in vertebral arteries. Takes 30 minutes for full effect. First ICA that was injected is then rechecked for improvement. Watch BP for hypotension
3. nicardipine: a dihydropiridine calcium channel blocker which acts preferentially on vascular smooth muscle more than cardiac smooth muscle. Restores vessels to at least 60% of normal diameter. 70% of those treated had no stroke on CT. May cause a drop in SBP, but not > 30%[188]. ***Rx*** intraarterial therapy: 10-40 mg per procedure

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30.4.6. Vasospasm management "protocol"

Table 30-10 shows a quick reference guide for vasospasm treatment.

ROUTINE MONITORING FOR ALL SAH PATIENTS

1. serial neuro exams
2. daily CBC with differential
3. transcranial doppler monitoring (where available): usually Mon-Weds-Fri

SPECIFIC TREATMENTS

Patients with clinical suspicion of vasospasm (DIND), or with transcranial doppler **(TCD)** increases of > 50 cm/sec or with absolute velocities > 200:

1. move patient to the ICU and placed on triple-H therapy for 6 hours if this is not already instituted
2. option: perfusion CT or MRI (if available)
3. if no response to 6 hrs of triple-H therapy, or if perfusion CT suggests vasospasm, patient is taken to angiography to confirm presence of vasospasm and for interventional neuroradiologic treatment (intraarterial verapamil, angioplasty…)

When a patient develops signs suggestive of vasospasm:

1. diagnostic measures (primarily to rule-out other causes of deficit)
   A. STAT non-contrast CT to rule-out hydrocephalus, edema, infarct or rebleed
   B. STAT bloodwork
      1. electrolytes to rule-out hyponatremia[97]
      2. CBC to assess rheology and rule-out sepsis or anemia
      3. ABG to rule out hypoxemia
   C. repeat TCD if available to detect changes indicative of vasospasm
2. treatment measures
   A. insert ICP monitor if ICP felt to be problematic, treat elevated ICP with mannitol or CSF drainage before institution hyperdynamic therapy **(HDT)** (caution: the diuresis from mannitol works against hypervolemia; also, exercise caution in lowering ICP with unsecured aneurysm, *see page 1044*)
   B. administer O_2 to keep pO_2 > 70 mm Hg
   C. activity: bed rest, HOB elevated to ≈ 30°
   D. TED hose and/or sequential compression boots
   E. A-line to monitor BP
   F. PA catheter to monitor PCWP and cardiac output when possible (central line to monitor CVP when PA catheter cannot be placed)
   G. monitoring labs:
      1. ABG and H/H daily
      2. serum and urine electrolytes and osmolalities q 12 hr (creatinine elevations may indicate peripheral ischemia from vasopressors)
      3. CXR daily
      4. frequent EKG

H. strict I & O measurements

I. continue calcium channel blockers (*see below*)

J. initiate hyperdynamic (triple-H) therapy (*see below*)

Table 30-10 QUICK REFERENCE GUIDE: Post-clipping management pertinent to vasospasm*

Condition	Management
No vasospasm • clinically intact • normal TCD	1. hemodynamics: A. normotension (SBP > 120 mm Hg) or 30% above baseline B. normal SVR (800-1200) 2. IVF: NS 200 ml/hr
Subclinical vasospasm • high TCDs (> 200 cm/sec) and/or radiographic evidence of vasospasm • clinically intact	1. monitors: PA-catheter, A-line 2. elderly and patients with CAD: EKG, cardiac echo & cardiac enzymes to assess left ventricle function 3. monitor for signs/symptoms of adverse effects of triple-H therapy (chest pain, pulmonary rhonchi, EKG changes…) 4. hemodynamics A. maintain SBP 160-220 mm Hg. If pressors necessary: 1. dopamine + levophed§ 2. add Neosynephrine§ if tachycardia > 140-150 BPM 3. if SBP still low: consider dobutamine§ if SVR > 800 and PCWP within desired parameters B. keep SVR WNL C. maintain PCWP 12-14 mm Hg 5. fluids: monitor I's & O's and serum sodium A. IVF: NS + Plasmanate 200-250 ml/hr (Δ to 1/2 NS if Na > 150) B. begin DDAVP§ if UO > 200 ml/hr **x** 4 hrs 6. hematocrit: keep Hct ≤ 33%
Clinical vasospasm • DIND • high TCDs and/or radiographic vasospasm	1. increase SBP to try and reverse DIND 2. increase PCWP to 18-21 mm Hg (monitor CXR for pulmonary edema) 3. refractory cases: consider cerebral angiography ± angioplasty (*see page 1049*) or ± intraarterial verapamil (*see page 1050*)

§ TRIPLE-H THERAPY QUICK REFERENCE (Hypertension, Hypervolemia, Hemodilution)

1. hypertension
   - A. dopamine (*see page 22*)
     1. start at 2.5 µg/kg/min (renal dose)
     2. titrate up to 15-20 µg/kg/min
   - B. levophed
     1. start at 1-2 µg/min
     2. titrate every 2-5 minutes: double the rate up to 64 µg/min, then increase by 10µg/min
   - C. Neosynephrine (phenylephrine): does not exacerbate tachycardia
     1. start at 5 µg/min
     2. titrate every 2-5 minutes: double the rate up to 64 µg/min, then increase by 10µg/min up to a max of 10 µg/kg
   - D. dobutamine: positive inotrope
     1. start at 5 µg/kg/min
     2. increase dose by 2.5 µg/kg/min up to a maximum of 20 µg/kg/min
2. hypervolemia
   - A. fluids: normal saline ± plasmanate: 200-250 ml/hr
   - B. DDAVP: antidiuretic (counteracts urinary loss of circulating fluid volume)
     1. 2-4 µg SQ q d in divided doses
     2. reduce or hold for volume overload or excessive hemodilution
3. hemodilution

A. target hematocrit (Hct): ≤ 33%
B. transfuse for Hct < 25%

* see text for details

HYPERDYNAMIC THERAPY (HDT) - "TRIPLE-H THERAPY"

AKA "triple-H" therapy (for: hypervolemia, hypertension and hemodilution)[189] or induced arterial hypertension. Elevating systemic blood pressure by expanding circulating blood volume has demonstrated benefit[190, 191], but may not reduce overall morbidity and mortality[192]. Inducing HTN may be risky with an unclipped ruptured aneurysm. In the case of multiple aneurysms, the risk of hemorrhage from a previously unruptured aneurysm appears low enough to justify volume expansion once the ruptured aneurysm has been clipped[193]. Initiating therapy before CVS is apparent may minimize morbidity from CVS[95, 194] (patients with SAH often develop hypovolemia early in their course[103, 195, 196], and once CVS is evident, changes have already occurred, some possibly irreversible).

PROTOCOL FOR HYPERDYNAMIC THERAPY (modified[190])

Monitors

- indwelling urinary catheter (Foley)
- A-line: essential
- PA catheter: highly recommended. Consider employing one with a pacing port in case this is needed to counteract reflex bradycardia. A catheter with continuous cardiac output **(cCO)** measuring capability is ideal, which avoids the need to inflate balloon periodically
- some centers monitor transcranial doppler **(TCD)**
- perfusion CT

Endpoints

✖ to avoid severe cerebral edema or hemorrhagic infarction, do not institute in patient who demonstrates massive edema or a large ischemic infarct coincident with the onset of DIND, especially within the first 6 days post-SAH[197]

- use fluids, pressors… (*see below*) to increase SBP in 15% increments until neurologically improved or the following endpoints all reached

- ◆ elevate CVP to 8-12 cm H_2O, or PCWP to 18-20 mm Hg[A] (for unclipped aneurysms: CVP 6-10 cm H_2O, PCWP 6-10 mm Hg)
- ◆ maximum BP in clipped aneurysms: SBP < 240 mm Hg, mean BP < 150 (for unclipped aneurysm: SBP < 160)
- ◆ reduction of elevated TCD readings back towards baseline

- then allow BP to fall to level required to sustain acceptable neurologic function
- if triple-H therapy fails, use endovascular techniques if available (*see page 1049*)

A. these CVPs and PCWPs are given as a guideline. It is best to determine what CVP or PCWP optimizes the individual patient's cardiac output, and then maintain that level

---

Methods of inducing hyperdynamic therapy

Proceed to each step only if needed to meet above endpoints or reverse neurologic deficit.

1. volume expansion: goal is euvolemia or very slight hypervolemia
   A. primary IV fluid is crystalloid, usually isotonic (e.g. NS)
   B. blood (whole or PRBC) when Hct drops < 40%
   C. colloid: plasma fraction or 5% albumin (at 100 ml/hr) to maintain 40% Hct (if Hct is > 40%, use crystalloids[84])
   D. mannitol 20% at 0.25 gm/kg/hr as a drip may improve rheologic properties of blood in the microcirculation (avoid hypovolemia from resultant diuresis)
   E. ✖ avoid hetastarch (Hespan®) and dextran which impair coagulation (*see page 1042*)
   F. replace urinary output **(U.O.)** with crystalloid (if Hct < 40%, then use 5% albumin, usually @ ≈ 20-25 ml/hr)
2. pressors: also see *Cardiovascular agents for shock*, page 22. A SBP of 100-220 may be required to reverse ischemic symptoms, and is generally safe with a clipped aneurysm in the absence of underlying ischemic heart disease
   A. dobutamine: a pure ß agonist. May improve blood flow in cerebral microcirculation at stable MAP. ***Rx***: start at 5 µg/kg/min and titrate to maximize cardiac output (usually 5-18 µg/kg/min)

B. dopamine may alternatively be used (*see page 22*)

C. if symptoms not reversed after 30-60 mins, add phenylephrine, an alpha agonist. ***Rx***: start at 2 μg/kg/min and titrate to maximize MAP (usually 2-15 μg/kg/min)

3. bradycardia (reflex vagal response) is treated with atropine 1 mg IM q 3-4 hrs to keep pulse 80-120 (or pace through PA catheter pacing port)
4. compensatory diuresis: replace U.O. with albumin (*see above*). Diuresis may be counteracted with vasopressin (Pitressin®). Caution needs to be exercised due to possible exacerbation of hyponatremia. Use either:

• aqueous vasopressin 5 U SQ titrate to urine output < 200 ml/hr

OR

• vasopressin IV drip, start at 0.1 U/min and titrate up to 0.5 U/min to keep urine output < 200 ml/hr

5. fludrocortisone (Florinef®) 2 mg/d (NB: this dose is ≈ 10 times higher than the homeostatic dose for adrenal replacement therapy, *see page 34*) or desoxycortisone 20 mg/d in divided doses
6. digitalis if vascular congestion seen on CXR accompanied by decreased cardiac output or ABG deterioration

Complications of hyperdynamic therapy:

1. intracranial complications[197]
   A. may exacerbate cerebral edema and increase ICP
   B. may produce hemorrhagic infarction in an area of previous ischemia
2. extracranial complications
   A. pulmonary edema in 17%
   B. 3 rebleeds (1 fatal)
   C. dilutional hyponatremia in 3%
   D. MI in 2%
   E. complications of PA catheter[198]:
      1. catheter related sepsis: 13%
      2. subclavian vein thrombosis: 1.3%
      3. pneumothorax: 1%
      4. hemothorax: may be promoted by coagulopathy from dextran[197]

Neurological outcome

The above protocol was used in 58 patients with vasospasm (22 unsecured aneurysm, 2 SAH of unknown etiology) with the following results: neurological

improvement occurred in 81%; temporary in 7%. No change was seen in 16%. 10% deteriorated.

CALCIUM CHANNEL BLOCKERS

Trials with calcium channel blockers

Calcium channel blockers **(CCB)** (AKA calcium antagonist) block the "slow-channel" of calcium influx which reduces the contraction of smooth and cardiac muscle, but does not affect skeletal muscle. It is thus theorized that the abnormal contraction of vascular smooth muscle that may contribute to vasospasm may be mitigated by the administration of CCBs.

CCBs may be more beneficial in neuroprotection than in preventing vasospasm. Their beneficial impact may derive from a number of possible effects:

1. increased red blood cell deformability (which improves blood rheology)
2. prevention of calcium entry into ischemic cells which may mediate the injury from cerebral infarction[199]
3. anti-platelet aggregating effect[200]
4. dilatation of collateral leptomeningeal arteries[201]

Agents presently available

1. **nimodipine** (Nimotop® - brand discontinued in U.S.): a CCB with preferential CNS action. Blocks dihydropyridine-sensitive (L-type) calcium channels. Does not alter radiographic vasospasm[202], and there is no statistically significant difference in mortality. However, outcome is improved[203].

   Rx: 60 mg PO or per NG q 4 hrs (monitor BP)[202, 204, 205] initiated within 96 hrs of SAH. Dosage is halved for liver failure. IV form is similarly effective[90] where available. Administer either for 21 days or until the patient is discharged home in good neurological condition, whichever occurs first[141]
2. **nicardipine** (Cardene®)[206]: initial trials with indicated a lower incidence of vasospasm in the highest dose group[207], however it has subsequently been shown to be no better than placebo in overall outcome (however, it may reduce the need for HDT). Given as an IV drip at 148 µg/kg/hr (high

dose[207]: 0.15 mg/kg/hr)

3. miscellaneous: nifedipine (20 mg PO start TID and increase to QID), diltiazem, and others. Systemic effects usually limit dosage. Less widely used in the U.S. since nimodipine was approved by the FDA in 1989

Side effects of CCBs

Possible side effects include:

1. systemic hypotension: may be mitigated by IV volume expansion
2. renal failure
3. pulmonary edema

30.4.7. Neurogenic stunned myocardium (NSM)

Key concepts:

> • impaired cardiac function (reduced ejection fraction) not attributable to underlying coronary artery disease or myocardial abnormalities. May be reversible
> • cardiac enzymes (troponin) tend to be lower than expected for the degree of myocardial impairment, distinguishes NSM from acute MI
> • putative mechanism: catecholamine surge (possibly in myocardial sympathetic nerves) as a result of hypothalamic stimulation or injury from the SAH
> • possible sequalae: hypotension, CHF, arrhythmias… all of which may further exacerbate cerebral ischemia
> • peak incidence: 2 days to 2 weeks post SAH
> • risk factors: higher Hunt and Hess grade
> • treatment: may include dobutamine (for SBP < 90 and low SVR) and/or milrinone (for SBP > 90 and increased SVR)

Previously AKA reversible postischemic myocardial dysfunction[105]. Classically seen in patients following cardiac surgery, and attributed to a defect in troponin-I (TnI)[106]. Some patients may develop myocardial hypokinesis following SAH[107]. May appear compatible with an MI on echocardiography, yet, troponin levels are typically lower (often < 2.8 ng/ml) than would be predicted given the level of myocardial impairment[108]. Peak incidence: 2 days to 2 weeks

post SAH. The condition reverses completely in most cases within about 5 days. However, ≈ 10% of patients may progress on to an actual MI.

Stroke volume and cardiac output are reduced. Hypotension does not always occur since the reduced cardiac output **(CO)** may be offset by an increase in SVR. However, the reduced CO may impair the ability to tolerate barbiturates administered for cerebral protection during early surgery due to their myocardial suppressant effect. Intraoperative TEE monitoring may be a useful guide for titrating pressors. The reduced CO may also impede the use of hyperdynamic therapy for vasospasm.

Arrhythmias & EKG changes

EKG changes in over 50% of cases of SAH and include: broad or inverted T-waves, Q-T prolongation, S-T segment elevation or depression, U-waves, premature atrial or ventricular contraction, SVT, V-flutter or V-fib[109], bradycardia. In some cases EKG abnormalities may be indistinguishable from an acute MI[110, 111].

Possible mechanism

Hypothalamic ischemia may lead to increased sympathetic tone and the resultant catecholamine surge may produce subendocardial ischemia[112] or coronary artery vasospasm[107]. The catecholamine surge appears to be more focal (i.e. in the heart) than systemic.

Treatment

Interventions that have been studied for increasing cardiac output in NSM[113, 114]:

- milrinone: used when SBP > 90 mmHg and normal SVR, or when the patient is on chronic beta blockers
- dobutamine: more effective with hypotension (SBP < 90 mmHg) and low SVR
- other options: stellate ganglion block, magnesium

30.5. Cerebral aneurysms

EPIDEMIOLOGY

Incidence difficult to estimate. Range of autopsy prevalence of aneurysms: 0.2-7.9% (variability depends on use of dissecting microscope, hospital referral and autopsy pattern, overall interest). Recent studies[208] indicate prevalence of 5%. Ratio of ruptured:un-ruptured (incidental) aneurysm is 5:3 to 5:6 (rough estimate is 1:1, i.e. 50% of these aneurysms rupture)[209]. Only 2% of aneurysms present during childhood[210].

ETIOLOGY

The exact pathophysiology of the development of aneurysms is still controversial. In contrast to extracranial blood vessels, there is less elastic in the tunica media and adventitia of cerebral blood vessels, the media has less muscle, the adventitia is thinner, and the internal elastic lamina is more prominent[211, 212]. This, together with the fact that large cerebral blood vessels lie within the subarachnoid space with little supporting connective tissue[213 (p 1644)] may predispose to the development of aneurysms. Aneurysms tend to arise in areas where there is a curve in the parent artery, in the angle between it and a significant branching artery, and point in the direction that the parent artery would have continued had the curve not been present[214].

The etiology of aneurysms may be:

- congenital predisposition (e.g. defect in the muscular layer of the arterial wall, referred to as a **medial gap**)
- "atherosclerotic" or hypertensive: presumed etiology of most saccular aneurysms, probably interacts with congenital predisposition described above
- embolic: as in atrial myxoma
- infectious (so called "mycotic aneurysms", *see page 1082*)
- traumatic (see *Traumatic aneurysms*, page 1081)
- associated with other conditions (*see below*)

LOCATION

Saccular aneurysms, AKA **berry aneurysms** are usually located on major named cerebral arteries at the apex of branch points which is the site of maximum hemodynamic stress in a vessel[215]. More peripheral aneurysms do occur, but tend to be associated with infection (mycotic aneurysms) or trauma. **Fusiform aneurysms** are more common in the vertebrobasilar system. Dissecting aneurysms should be categorized with arterial dissection (*see page 1160*).

Saccular aneurysms location:

- 85-95% in carotid system, with the following 3 most common locations:
  - ACoA (single most common): 30% (ACoA & ACA more common in males)
  - p-comm: 25%
  - middle cerebral artery (MCA): 20%
- 5-15% in posterior circulation (vertebro-basilar)
  - ≈ 10% on basilar artery: basilar bifurcation, AKA basilar tip, is the most common, followed by BA-SCA, BA-VA junction, AICA
  - ≈ 5% on vertebral artery: VA-PICA junction is the most common
- 20-30% of aneurysm patients have multiple aneurysms[216] (*see page 1080*)

PRESENTATION OF ANEURYSMS

MAJOR RUPTURE

The most frequent presentation

1. most commonly produces SAH (*see page 1034*), which may be accompanied by:
2. intracerebral hemorrhage: occurs in 20-40% (more common with aneurysms distal to the Circle of Willis, e.g. MCA aneurysms)
3. intraventricular hemorrhage: occurs in 13-28%[217] (*see below*)
4. subdural blood in 2-5%

Intraventricular hemorrhage

See page 1228 for other etiologies of intraventricular hemorrhage **(IVH)**.

IVH occurs in 13-28% of ruptured aneurysms in clinical series (higher in autopsy series)[217] and appears to carry a worse prognosis (64% mortality)[217]. The size of the ventricles on admission was the most important prognosticator (large vents being worse). Patterns that may occur:

1. distal PICA aneurysms: may rupture directly into 4th ventricle through the foramen of Luschka[218]
2. a-comm aneurysm: it has been asserted that IVH occurs from rupture through the lamina terminalis into the anterior 3rd or lateral ventricles, however, this is not always borne out at the time of surgery
3. distal basilar artery or carotid terminus aneurysms: may rupture through

the floor of the 3rd ventricle (rare)

Presentation other than major rupture

May be thought of as possible “warning signs”.

1. mass effect
   A. giant aneurysms: including brain stem compression producing hemiparesis and cranial neuropathies
   B. cranial neuropathy (average latency from symptom to SAH was 110 days[B]) including:
      1. oculomotor (3rd nerve) palsy **(ONP)**: occurs in ≈ 9% of p-comm aneurysms[219A], less common with basilar apex aneurysm. Symptoms of ONP may include:
         a. extraocular muscle palsy (eye deviates “down and out” → diplopia)
         b. ptosis
         c. dilated unreactive pupil (★ non-pupil-sparing third nerve palsy is the classic finding of 3rd nerve compression - *see page 835*)

The development of a third nerve palsy in a patient with an unruptured aneurysm is a medical emergency as it probably results from aneurysmal expansion and may portend impending rupture.

      2. visual loss due to[220]
         a. compressive optic neuropathy with ophthalmic artery aneurysms: characteristically produces nasal quadrantanopsia
         b. chiasmal syndromes due to ophthalmic, a-comm, or basilar apex aneurysms
      3. facial pain syndromes in the ophthalmic or maxillary nerve distribution that may mimic trigeminal neuralgia can occur with intracavernous or supraclinoid aneurysms[220, 221]
   C. intra- or suprasellar aneurysm producing endocrine disturbance[222] due to pituitary gland or stalk compression
2. minor hemorrhage: warning or sentinel hemorrhage (see *Headache*, page 1035). This group had the shortest latency (10 days) between symptom and SAH[B]
3. small infarcts or transient ischemia due to distal embolization (including amaurosis fugax, homonymous hemianopsia…)[220]: average latency from symptom to SAH was 21 days[B]

4. seizures: at surgery, an adjacent area of encephalomalacia may be found[220]. The seizures may arise as a result of localized gliosis and do not necessarily represent aneurysmal expansion as there is no data to indicate an increased risk of hemorrhage in this group
5. headache[220] without hemorrhage: abates after treatment in most cases
   A. acute: may be severe and "thunderclap" in nature[36], some describe as "worst headache of my life". Has been attributed to aneurysmal expansion, thrombosis, or intramural bleeding[32], all without rupture
   B. present for ≥ 2 weeks: unilateral in about half (often retro-orbital or periorbital), possibly due to irritation of overlying dura. Diffuse or bilateral in the other half, possibly due to mass effect → increased ICP
6. incidentally discovered (i.e. asymptomatic, e.g. those found on angiography, CT or MRI obtained for other reasons)

A. ruptured and unruptured p-comm aneurysms

B. the average latency quoted for some of these symptoms comes from a retrospective study of patients presenting with SAH who were identified as having a warning symptom[26]

30.5.1. Conditions associated with aneurysms

- autosomal dominant polycystic kidney disease: (*see below*)
- fibromuscular dysplasia **(FMD)**: prevalence of aneurysms in renal FMD is 7%, in aortocranial FMD 21%
- arteriovenous malformations **(AVM)** including moyamoya disease (see *AVMs and aneurysms*, page 1100)
- connective tissue disorders[223]:
  A. Ehlers-Danlos, especially type IV (deficient collagen type III) which also has a high rate of arterial dissection including with angiography or coiling
  B. Marfan syndrome (*see page 1161*)
  C. pseudoxanthoma elasticum
- multiple other family members with intracranial aneurysms. **Familial intracranial aneurysm syndrome (FIA)**: 2 or more relatives, third degree or closer, harbor radiographically proven aneurysms (also, see *Familial aneurysms*, page 1080)

• coarctation of the aorta[224]
• Osler-Weber-Rendu syndrome
• atherosclerosis[29]
• bacterial endocarditis

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Adult polycystic kidney disease is seen in 1 of every 500 autopsies, and approximately 500,000 people in the U.S. carry the mutant gene for autosomal dominant polycystic kidney disease **(ADPKD)**. Renal function is usually normal during the first few decades of life, with progressive chronic renal failure ensuing. HTN is a common sequelae. Transmission is autosomal dominant, with 100% penetrance by 80 yrs of age[225]. Cystic disease of other organs may occur (viz.: liver in ≈ 33%, and occasionally lung, pancreas)[226].

Reported prevalence of aneurysms with ADPKD: 10-30%[227], with 15% being a reasonable estimate[228]. Most were located on the MCA, with multiple aneurysms present in 31%[229]. In addition to the increased incidence of aneurysms, there appears to be an increased risk of rupture[230], with 64% occurring before age 50. As a result, patients with ADPKD carry a 10-20 fold increased risk of SAH compared to the general population[231]. Aneurysms are rarely detectable before age 20 years. The average rate of rupture of incidental aneurysms is ≈ 2%/yr (see *Unruptured aneurysms*, page 1077).

Recommendations

Using the above statistics, together with the life expectancy of patients with ADPKD, and other estimations (of operative morbidity and mortality, etc.), results of decision analysis is that arteriography <u>not</u> be routinely employed in patients older than 25 yrs[227]. However, patients with symptoms possibly due to unruptured aneurysms, and those with SAH, should undergo angiography and subsequent surgical repair of any aneurysms discovered (especially those > 1 cm diameter). A decision analysis study[228] determined that screening with <u>MRA</u> was beneficial compared to treating patients once they became symptomatic. In a young patient with ADPKD with either a history of aneurysms or a kindred of ADPKD with aneurysms, repeat screening may be effectively repeated every ≈ 2-3 years (in a kindred of ADPKD without aneurysms, every 5-20 yrs was recommended)[228].

30.6. Treatment options for aneurysms

The optimal treatment for an aneurysm depends on the condition of the patient, the anatomy of the aneurysm, the ability of the surgeon, and must be weighed against the natural history of the condition. Also, treatment of the aneurysm facilitates treatment of vasospasm, should it occur.

Natural history:

1. risk of bleeding into subarachnoid space
   A. for ruptured aneurysms: this is the risk of *rebleeding*: *see page 1043*
   B. for unruptured aneurysms: *see page 1077*
   C. for cavernous carotid artery aneurysms: this risk is low (*see page 1079*)
2. **spontaneous thrombosis** of an aneurysm is a rare occurrence[232-234] (estimates in *autopsy* series is 9-13%[234]). However they may reappear[235, 236], and delayed rupture may occur sometimes even years later

Although still controversial, endovascular treatment should be initially considered in treating amenable ruptured aneurysms. For unruptured aneurysms, *see page 1077*.

Therapies that do not directly address the aneurysm

The hope here is that the aneurysm will not bleed and that it will thrombose (*see above*).

1. continue medical management initiated on admission: i.e. control of HTN, continue calcium-channel blockers, stool softeners…continue bed rest for ≈ 1 week then allow bedside commode
2. treatment options generally not used
   A. antifibrinolytic therapy (e.g. ε-aminocaproic acid **(EACA)**): ✖ NB: NOT USED. Reduces rebleeding, but increases the incidence of arterial vasospasm and hydrocephalus[120]
   B. serial LPs: an historical treatment[237], may increase the risk of aneurysmal rupture

Endovascular techniques to treat the aneurysm

1. thrombosing the aneurysm:
   A. "coiling" with Guglielmi electrolytically detachable coils (*see below*)
   B. Onyx HD 500 (*see page 1102*) has been used for wide-necked or giant ICA aneurysms[238]. Out of 22 patients, there was 1 parent ICA stenosis and 2 ICA occlusions caused by Onyx migration
2. trapping: effective treatment requires distal AND proximal arterial interruption, usually by endovascular techniques[239], occasionally by direct surgical means (ligation or clip occlusion), or some combination. May also incorporate vascular bypass (e.g. EC-IC bypass) to maintain flow distal to trapped segment[240]
3. proximal ligation (hunterian ligation): useful for giant aneurysms[241, 242]. For non-giant aneurysms provides little benefit and adds the risk of thromboembolism (which may be reduced by occluding the CCA rather than the ICA[242]). May also elevate the risk of developing aneurysms in the contralateral circulation[243]

Surgical treatment options for aneurysms

1. clipping: the surgical gold standard. Surgical placement of a clip across the neck of the aneurysm to exclude the aneurysm from the circulation (*see below*) without occluding normal vessels
2. wrapping or coating the aneurysm: although this should never be the goal of surgery, situations may arise in which there is little else that can be done (e.g. fusiform basilar trunk aneurysms, aneurysms with significant branches arising from the dome, or part of the neck within the cavernous sinus)
   A. with muscle: the first method used to surgically treat an aneurysm[244] (the patient described died from rebleeding)
   B. with cotton or muslin: popularized by Gillingham[245]. Analysis of 60 patients showed that 8.5% rebled in ≤ 6 mos, and the annual rebleeding rate was 1.5% thereafter[246] (similar to natural history)
   C. with plastic resin or other polymer: may be slightly better than muscle or gauze[247]. One study with long follow-up found no protection from rebleeding during the first month, but thereafter the risk was slightly lower than the natural history[247]. Other studies show no difference from natural course[248]
   D. Teflon and fibrin glue[249]

Treatment decisions: coiling vs. clipping

Factors that favor surgical clipping:

1. younger age: lower risk of surgery, and lower lifetime risk of recurrence than with coiling
2. middle cerebral artery (MCA) bifurcation aneurysms
3. giant aneurysms: > 20 mm diameter)[250]. High recanalization rate with coiling
4. symptoms due to mass effect: clipping[251, 252] may be better than coiling. In 13 patients with p-comm aneurysms and oculomotor nerve (3rd nerve) palsy **(ONP)**, 6 of 7 patients clipped vs. 2 of 6 with coiling recovered completely[219]. Partial ONP improved with either treatment, but complete ONP recovered in 3 of 4 patients clipped vs. 0 of 3 coiled[219]
5. small aneurysm: < 1.5-2 mm diameter 250. Higher incidence of intraprocedural rupture with coiling
6. wide aneurysm neck[250]
7. patients with residual filling of the aneurysm after coiling since there is significant risk of rebleeding

Factors favorable for coiling:

1. elderly patients (> 75 yrs): there appears to be a significant reduction in morbidity with coiling compared to clipping
2. poor clinical grade
3. inaccessible ruptured aneurysms
4. aneurysm configuration[74]:
   A. dome-to-neck ratio (AKA fundus-to-neck ratio) ≥ 2
   B. and an absolute neck diameter < 5 mm
5. posterior circulation aneurysms
6. patients on Plavix®
7. may be considered in cases where there is a failure of attempted clipping, or with aneurysms that are technically difficult to clip (a category that is very vague and varies widely with the experience of the neurosurgeon[253])

Controversial areas with coiling:

1. unruptured aneurysms: unruptured M1-M2 junction MCA aneurysms are often difficult to coil because of a branch near the neck[254]

ELECTROLYTICALLY DETACHABLE COILS ***(EDC)***

Electrolytically detachable platinum coils AKA Guglielmi detachable coils, or simply "coils", placed either during open surgery or, more commonly, via endovascular techniques[255-257]. For indications for coiling vs. clipping, *see above*. Goals of coiling:

1. to promote thrombosis of the aneurysmal sac to prevent (re)bleeding
2. to reduce symptoms of mass effect[258], if any (clipping still appears to be superior to coiling for this - *see above*)

Available data: There has been no long-term prospective randomized trial to compare coiling to microsurgery **(MS)**[253, 259]. The largest trial to date, the International Subarachnoid Hemorrhage Aneurysm Trial **(ISAT)**[260] had the important shortcomings detailed in *Table 30-11*. Also, still unresolved: coiling vs. MS for *unruptured* aneurysms.

Results

Procedural morbidity rate of coiling (mostly aneurysmal rupture) ≈ 4%,; mortality = 1%[261].

Results may be reported as occlusion rates or in terms of recurrence of SAH. Depending on criteria and timing of follow-up, MS fares better than coiling with occlusion rates and prevention of recurrent SAH.

Results of ISAT study: at 1 year follow-up, there was an absolute reduction of risk of having a poor outcome by 7% with coiling (24%) than with MS (31%).

Table 30-11 Methodological short-comings of ISAT

1. only 20% of 9559 patients presenting with SAH were randomized* • selection could introduce bias • more nonrandomized patients underwent MS than EDC • guidelines not provided for which patients to consider for EDC 2. most study centers were located in Europe, Australia & Canada 3. the expertise of the surgeons and the interventionalists were not reported and were not necessarily comparable 4. the following features are not entirely representative of SAH patients at large • 80% of patients were in good clinical condition (H&H grade 1 or 2) • 93% of aneurysms were ≤ 10 mm diameter • 97% were in the anterior circulation 5. rebleeding rate: after EDC (2.4%) or MS (1.0%) was high for both groups, and the difference could be more significant beyond the 1 year follow-up provided

* most SAH patients were referred specifically for MS or EDC. The only patients that were were randomized were those for whom a panel decided it was not clear which procedure would be superior.

Out-comes were not provided for non-randomized patients

Treatment failures may be due to:

1. early failure
   A. intraprocedural rupture
   B. vasospasm preventing endovascular treatment (< 1.5%)
   C. failure to achieve initial obliteration: 39% are completely obliterated, 46% are ≥ 95% occluded, and 15% are < 95% occluded[262]. Of aneurysms not initially occluded[262]:
      1. 46% progressively thrombosed
      2. 26% showed stable neck remnants
      3. 28% showed enlargement of residual neck
2. late failure
   A. failure of partially obliterated aneurysms to go on to thrombose
   B. coil compaction
   C. enlargement of residual neck
   D. recanalization of aneurysm: 1.8% risk[262]

Recurrent SAH following coil placement

1. ISAT study: 0.16% at 1 year[260]
2. 5% incidence of SAH (rebleeding) within 6 months of treatment (high compared to MS) in one series of 75 patients with acutely ruptured aneurysms[250]
3. in another series of 141 coiled aneurysms[262] (42% incidental, 41% acutely ruptured): 1 patient rebled within 6 months (1.7% of the ruptured group)

Repeat treatment: Data on long-term efficacy is lacking. At least 20% of patients with relatively short follow-up needed retreatment in one series[263]. In the ISAT study, more than 4 times as many patients undergoing coiling needed additional procedures than did the MS group[260].

Stent assisted coiling: Stent assisted coiling should rarely be used with ruptured aneurysms because of the necessity of dual antiplatelet therapy (ASA/Plavix) which increases the morbidity of subsequent ventriculostomy, shunting…

Treatment of aneurysmal rupture during coiling

1. inflate balloon if balloon assisted coiling
2. immediately reverse anticoagulation. 50 mg of protamine should be available during the procedure

3. continue to pack coils as rapidly as possible
4. insert an extraventricular drain (EVD)

30.7. Timing of aneurysm surgery

Controversy exists between so-called "early surgery" (generally, but not precisely defined as ≤ 48-96 hrs post SAH) and "late surgery" (usually ≥ 10-14 days post SAH). Also *see page 1074* for timing issues related to basilar bifurcation aneurysms.

Early surgery advocated for the following reasons:

1. if successful, virtually eliminates the risk of rebleeding which occurs most frequently in the period immediately following SAH (see *Rebleeding*, page 1043)
2. facilitates treatment of vasospasm which peaks in incidence between days 6-8 post SAH (never seen before day 3) by allowing induction of arterial hypertension and volume expansion without danger of aneurysmal rupture
3. allows lavage to remove potentially vasospasmogenic agents from contact with vessels (including use of thrombolytic agents, *see page 1048*)
4. although operative mortality is higher, overall patient mortality is lower[264]

Arguments against early surgery, in favor of late surgery include:

1. inflammation and brain edema are most severe immediately following SAH
   A. this necessitates more brain retraction
   B. at the same time this softens the brain making retraction more difficult (retractors have more tendency to lacerate the more friable brain)
2. the presence of solid clot that has not had time to lyse impedes surgery
3. the risk of intraoperative rupture is higher with early surgery
4. possible increased incidence of vasospasm following early surgery from mechanotrauma to vessels

Factors that favor choosing early surgery include:

1. good medical condition of patient
2. good neurologic condition of patient (Hunt and Hess **(H&H)** grade ≤ 3)
3. large amounts of subarachnoid blood, increasing the likelihood and severity of subsequent vasospasm (see *Table 30-6*, page 1046). Having the

aneurysm clipped permits use of hyperdynamic therapy for vasospasm (see *Hyperdynamic therapy (HDT) - "Triple-H therapy"*, page 1052)
4. conditions that complicate management in face of unclipped aneurysm: e.g. unstable blood pressure; frequent and/or intractable seizures
5. large clot with mass effect associated with SAH
6. early rebleeding, especially multiple rebleeds
7. indications of imminent rebleeding: (*see below*)

Factors that favor choosing delayed surgery (10-14 days post SAH) include:
1. poor medical condition and/or advanced age of patient (age may not be a separate factor related to outcome, when patients are stratified by H&H grade[265])
2. poor neurologic condition of patient (H&H grade $\geq$ 4): controversial. Some say the risk of rebleeding and its mortality argues for early surgery even in bad grade patients[266] since denying surgery on clinical grounds may result in withholding treatment in some patients who would do well (54% of H&H grade IV and 24% of H&H grade V patients had favorable outcome in one series[265]). Some data show no difference in surgical complications in good and bad grade patients with anterior circulation aneurysms[267]
3. aneurysms difficult to clip because of large size, or difficult location necessitating a lax brain during surgery (e.g. difficult basilar bifurcation or mid-basilar artery aneurysms, giant aneurysms)
4. significant cerebral edema seen on CT
5. the presence of active vasospasm

Conclusions

There is insufficient Class 1 data to make any firm conclusions. Therefore the following is based on trials that are non-randomized, etc.
1. there is an overall trend towards better outcome with early surgery than with later surgery, however, the advantage of early surgery (reduced rebleeding) is at least partially offset by the disadvantages of early surgery[268] (*see above*)
2. outcomes seem worse when surgery is performed between days 4-10 after SAH (the "vasospastic interval") than if performed early or late

IMMINENT ANEURYSM RUPTURE

Findings that may herald impending aneurysm rupture include:

1. progressing cranial nerve palsy e.g. development of 3rd nerve palsy with p-comm aneurysm (traditionally regarded as an indication for urgent treatment) (*see page 1056*)
2. increase in aneurysm size on repeat angiography
3. beating aneurysm sign[269]: pulsatile changes in aneurysm size between cuts or slices on imaging (may be seen on angiography, MRA, or CTA)

30.8. General technical considerations of aneurysm surgery

The goal of aneurysm surgery is to prevent rupture or further enlargement of the aneurysm, while at the same time preserving all normal vessels and minimizing injury to brain tissue and cranial nerves. This is usually accomplished by excluding the aneurysm from the circulation with a clip across its neck. Placing the clip too low on the aneurysm neck may occlude the parent vessel, while too distal placement may leave a so-called “aneurysmal rest” which is not benign (*see below*).

See *Intraoperative aneurysm rupture* below for general measures to reduce the risk of this complication during surgery.

Aneurysmal rest

When a portion of the aneurysm neck is not occluded by a surgical clip, it is referred to as an aneurysmal rest. A “dogear” occurs when a clip is angled to leave part of the neck at one end, and obliterates the neck at the other. Rests are not innocuous, even if only 1-2 mm, because they may later expand and possibly rupture years later, especially in younger patients[270]. The incidence of rebleeding was 3.7% in one study, with an annual risk of 0.4-0.8% during the observation period of 4-13 yrs[271]. Patients should be followed with serial angiography, and any increase in size should be treated by reoperation or endovascular techniques if possible.

BOOKING THE CASE - CRANIOTOMY: FOR ANEURYSM

Also see defaults & disclaimers (*page v*).

1. position: (depends on location of aneurysm), radiolucent head-holder
2. intraoperative angiography (optional)
3. equipment: microscope (with ICG capability if used)
4. blood: type and cross 2 U PRBC
5. post op: ICU
6. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the skull to place a permanent clip on the base of the aneurysm to prevent future bleeding, intraoperative angiogram, possible placement of external (ventricular) drain, possible lumbar drain
   B. alternatives: nonsurgical management, endovascular treatment only for aneurysms that are candidates
   C. complications: (usual craniotomy complications - *see page v*) *plus* (the following are not really complications of surgery but are possible developments) post-op vasospasm, hydrocephalus, formation of new aneurysms

SURGICAL EXPOSURE

To avoid excessive brain retraction, surgical exposure requires sufficient bony removal and adequate brain relaxation (*see below*).

BRAIN RELAXATION

More critical for ACoA and basilar tip than for easier to reach aneurysms such as pcomm or MCA…. Techniques include:

1. hyperventilation
2. CSF drainage: provides brain relaxation and a field dry of CSF, and removes blood & blood breakdown products. ✖ CSF drainage <u>before</u> opening the dura is associated with an increased risk of aneurysmal rebleeding (*see page 1043*)
   A. ventriculostomy: risks include seizures, bleeding from catheter insertion, infection (ventriculitis, meningitis), possible increased risk of vasospasm
      1. placed pre-op in cases of acute post-SAH hydrocephalus (*see page 1044*)
      2. placed intra-op

B. lumbar spinal drainage (*see below*)

C. intraoperative drainage of CSF from cisterns

3. diuretics: mannitol and/or furosemide. Although proof is lacking, lowering ICP by this or any means may theoretically increase the risk of rebleeding[272]

Lumbar spinal drainage

May be inserted with Tuohy needle following induction of anesthesia (to minimize BP elevation), prior to final positioning. CSF is gradually withdrawn by the anesthesiologist only after the dura is opened (to minimize chances of intraoperative aneurysmal bleeding), usually a total of 30-50 cc are removed in ≈ 10 cc aliquots.

Risks include[129]: aneurysmal rebleeding (≤ 0.3%), back pain (10%, may be chronic in 0.6%), catheter malfunction preventing CSF drainage (< 5%), catheter fracture or laceration resulting in retained catheter tip in the spinal subarachnoid space, post-op CSF fistula, spinal H/A (may be difficult to distinguish from post-craniotomy H/A), infection, neuropathy (from nerve root impingement with needle), epidural hematoma (spinal and/or intracranial).

CEREBRAL PROTECTION DURING SURGERY

PATHOPHYSIOLOGY OF CEREBRAL ISCHEMIA

The **cerebral metabolic rate of oxygen consumption (CMRO$_2$)** (*see page 1010*) arises from neurons utilizing energy for two functions: 1) maintenance of cell integrity (homeostasis) which normally accounts for ≈ 40% of energy consumption, and 2) conduction of electrical impulses. Occlusion of an artery produces a central core of ischemic tissue where the CMRO$_2$ is not met. The oxygen deficiency precludes aerobic glycolysis and oxidative phosphorylation. ATP production declines and cell homeostasis cannot be maintained, and within minutes irreversible cell death occurs; a so-called cerebral infarction. Surrounding this central core is the **penumbra**, where collateral flow (usually through leptomeningeal vessels) provides marginal oxygenation which may impair cellular function without immediate irreversible damage. Cells in the penumbra may remain viable for hours.

CEREBRAL PROTECTION BY INCREASING THE ISCHEMIC TOLERANCE OF THE CNS

1. drugs that mitigate the toxic effects of ischemia without reducing CMRO$_2$

    A. calcium channel blockers: nimodipine, nicardipine, flunarizine
    B. free radical scavengers: superoxide dismutase, dimethylthiourea, lazaroids, barbiturates, Vitamin C
    C. mannitol: although not a cerebral protectant *per se*, it may help re-establish blood flow to compromised parenchyma by improving the microvascular perfusion by transiently increasing CBV and decreasing blood viscosity
2. reduction of $CMRO_2$
    A. by reducing the electrical activity of neurons: titrating these agents to a isoelectric EEG reduces $CMRO_2$ by up to a maximum of ≈ 50%
        1. barbiturates: in addition to reducing $CMRO_2$, they also redistribute blood flow to ischemic cortex, quench free radicals, and stabilize cell membranes. For dosing of thiopental, *see below*
        2. isoflurane (*see page 2*): shorter acting and less myocardial depression than with barbiturates
    B. by reducing the maintenance energy of neurons: no drugs developed to date can accomplish this, only **hypothermia** has any effect on this. Below mild hypothermia, extracerebral effects must be monitored (*see page 880*)
        1. even **mild hypothermia** (core temperatures down to 33° C) has beneficial effects
        2. **moderate hypothermia**: 32.5-33° C has been used for head injury
        3. **deep hypothermia** to 18° C permits the brain to tolerate up to 1 hour of circulatory arrest
        4. **profound hypothermia** to < 10° C allows several hours of complete ischemia (the clinical usefulness of this has not been substantiated)

ADJUNCTIVE CEREBRAL PROTECTION TECHNIQUES USED IN ANEURYSM SURGERY

1. systemic hypotension
    A. usually used during final approach to aneurysm and during manipulation of aneurysm for clip application
    B. theoretical goals
        1. to reduce turgor of aneurysm facilitating clip closure, especially with atherosclerotic neck
        2. to decrease transmural pressure (*see page 1044*) to reduce the risk of intraoperative rupture

C. danger of hypoxic injury to other organs and brain (including areas of impaired autoregulation as well as normal areas). Because of this, some surgeons avoid this method

2. "focal" hypotension: using temporary aneurysm clips (specially designed with low closing force to avoid intimal injury) placed on parent vessel (small perforators will not tolerate temporary clips without injury)
   A. used in conjunction with methods of cerebral protection against ischemia
   B. may be combined with systemic hypertension to increase collateral flow
   C. the proximal ICA can tolerate an hour or more of occlusion in some cases, whereas the perforator bearing segments of the MCA and the basilar apex may tolerate clipping for only a few minutes
   D. in addition to the risk of ischemia, there is the risk of intravascular thrombosis and subsequent release of emboli upon removal of the clip
3. circulatory arrest, utilized in conjunction with deep hypothermia
   A. candidates include patients with large aneurysms that contain significant atherosclerosis and/or thrombosis that impedes clip closure and a dome that is adherent to vital neural structures

SYSTEMATIC APPROACH TO CEREBRAL PROTECTION[273]

The following factors may mandate the use of temporary clips (and associated techniques of cerebral protection): giant aneurysm, calcified neck, thin/fragile dome, adherence of dome to critical structures, vital arterial branches near the aneurysm neck, intraoperative rupture. Aside from giant aneurysms, most of these factors may be difficult to identify pre-op. Therefore, Solomon provides some degree of cerebral protection to all patients undergoing aneurysm surgery.

1. spontaneous cooling is permitted during surgery, which usually results in a body temperature of 34° C by the time that dissection around the aneurysm begins
2. if temporary clipping is utilized
   A. if a long segment of the ICA is being trapped, administer 5000 U IV heparin to prevent thrombosis and subsequent emboli
   B. < 5 mins temporary clip occlusion: no further intervention
   C. up to 10 or 15 mins occlusion: administer thiopental 5 mg/kg loading bolus, followed by drip infusion titrated to burst suppression on

compressed spectral array EEG

D. > 20 mins occlusion: not tolerated (except possibly ICA proximal to pcomm), terminate operation if possible and plan repeat operation utilizing
   1. deep hypothermic circulatory arrest (*see above*)
   2. endovascular techniques
   3. bypass grafting around the segment to be occluded

POSTOPERATIVE ANGIOGRAPHY

Due to the fact that unexpected findings (aneurysmal rest, unclipped aneurysm, or major vessel occlusion) were seen on 19% of post-op angiograms (the only predictive factor identified was a new post-op deficit, which signalled major vessel occlusion) the use of routine post-op angiography has been recommended[274].

SOME DRUGS USEFUL IN ANEURYSM SURGERY

propofol (Diprivan®) **DRUG INFO**

May be used to achieve burst suppression[275] with shorter duration of action than other barbiturates. Results are preliminary, further investigation is needed to demonstrate the degree of neuroprotection. Has been reported at doses 170 µg/kg/min for neuroprotection[276] (if tolerated) but this may be risky. May also be used as a continuous drip for sedation (*see page 24*), and for ICP management (*see page 885*). Reverses rapidly upon discontinuation (usually within 5-10 minutes).

SIDE EFFECTS: possible anaphylactic reaction with angioneurotic edema (angioedema) of the airways[277], Propofol Infusion syndrome (*see page 25*).

30.8.1. Intraoperative aneurysm rupture

EPIDEMIOLOGY

Reported rates of intraoperative aneurysm rupture **(IAR)** range from ≈ 18% in the cooperative study (1963-1978)[278] to 40% in a more recent series[279]. Although rupture rate may be higher in early surgery than with late surgery[279], other series found no difference[280].

Morbidity and mortality for patients experiencing significant IAR is ≈ 30-35% (vs. ≈ 10% in the absence of this complication), although IAR may primarily affects outcome when it occurs during induction of anesthesia or opening of dura[279].

For aneurysm rupture during coiling, *see page 1060*.

Prevention of intraoperative rupture

Presented as a list here to be incorporated into general operative techniques.

1. prevent hypertension from catecholamine response to pain:
   A. insure deep anesthesia during headholder pin placement and skin incision
   B. consider local anesthetic (without epinephrine) in headholder pin-sites and along incision line
2. minimize increases in transmural pressure: reduce MAP to slightly below base-line just prior to dural opening
3. reduce shearing forces on aneurysm during dissection by minimizing brain retraction:
   A. radical removal of sphenoid wing for circle of Willis aneurysms
   B. reduce brain volume by a number of mechanisms: diuretics (mannitol, furosemide), CSF drainage through lumbar subarachnoid drain at the time of dural incision, hyperventilation
4. reduce risk of large tear in aneurysm fundus or neck:
   A. utilize sharp dissection in exposing aneurysm and in removing clot from around aneurysm
   B. whenever possible, completely mobilize and inspect aneurysm before attempting clip application

Details of intraoperative rupture

Rupture can occur during any of the three following stages of aneurysm surgery[281]:

A. initial exposure (predissection)
   1. rare. Brain can become surprisingly tight even when bleeding seems to be into open subarachnoid space. Usually carries poor prognosis
   2. possible causes:
      A. vibration from bone work: dubious
      B. increasing transmural pressure upon opening the dura
      C. hypertension from catecholamine response to pain (*see above*)

3. management tactics:
   A. have anesthesiologist radically drop BP
   B. control bleeding (with anterior circulation aneurysms) by placing temporary clip across ICA as it exits from cavernous sinus, or if not possible then compress ICA in patient's neck through drapes
   C. if necessary to gain control, resect portions of frontal or temporal lobe

B. dissection of the aneurysm: accounts for the majority of IARs, two basic types:
1. tears caused by blunt dissection
   A. tends to be profuse, proximal to the neck, and difficult to control
   B. do not attempt definitive clipping unless adequate exposure has been achieved (which is usually not the case with these tears)
   C. **temporary clipping**: this step is often necessary in this situation, after the temporary clip is in place return the MAP to normal and administer neuroprotective agent (e.g. propofol)
   D. once the temporary clip is in place, it is better to take a few extra moments to improve the exposure and apply a well placed permanent clip instead of hastily clipping and trying to restore circulation
   E. microsutures may need to be placed to close any portion of the tear that extends onto the parent vessel
2. laceration by sharp dissection
   A. tend to be small, often distally on fundus, and usually easily controlled by a single suction
   B. may respond to gentle tamponade with a small cottonoid
   C. may shrink down with repeated low current strokes with the bipolar (avoid the temptation to use continuous high current)

C. clip application: bleeding at this point is usually due to either
1. inadequate exposure of aneurysm: clip blade may penetrate unseen lobe of aneurysm. Similar to tears caused by blunt dissection (*see above*). Bleeding worsens as clip blades become approximated
   A. prompt opening and removal of clip at the first hint of bleeding may minimize the extent of the tear
   B. utilize 2 suckers to determine if definitive clipping can be done, or what is more common, to allow temporary clipping (*see above*)
2. poor technical clip application: tends to abate as clip blades become approximated. Inspect the blade tips for the following:
   A. to be certain that they span the breadth of the neck. If not, a second

longer clip is usually applied parallel to the first, which may then be advanced

B. to verify that they are closely approximated. If not, tandem clips may be necessary, and sometimes multiple clips are needed

30.9. Aneurysm recurrence after treatment

Incompletely treated aneurysms may increase in size and/or bleed. This includes aneurysms that are clipped or coiled where there is still aneurysm filling, as well as a persistent aneurysm rest or a neck (*see page 1061*). While most aneurysm rests appear to be stable, there is a small subset that may enlarge or rupture[282].

Additionally, even an aneurysm that has been completely obliterated may recur, and therefore one has to consider the *durability* of treatment. The risk of recurrence of a completely clipped aneurysm is ≈ 1.5% at 4.4 years[282].

Table 30-12 Follow-up schedule for treated aneurysms

Perform indicated study at the following times after treatment	
Coiled aneurysms	**Clipped aneurysms**
Study: CTA or gad-MRA*	**Study: CTA**
6 mos	1 year
1.5 years	5 years
3.5 years	every 10 years thereafter
? every 5-10 years (as with clipped aneurysms)	

* gad-MRA indicates gadolinium MRA which is more sensitive here than TOF-MRA (*see page 132*). Use the same modality for each follow-up to facilitate accurate comparison

FOLLOW-UP AFTER ANEURYSM TREATMENT

Based on the above, together with the small risk of de novo aneurysm formation[282], there is a trend to indefinitely follow patients with known aneurysms. One suggested follow-up schedule is shown in *Table 30-12*.

30.10. Aneurysm type by location

30.10.1. Anterior communicating artery aneurysms

The single most common site of aneurysms presenting with SAH[283]. May additionally present with diabetes insipidus **(DI)** or other hypothalamic dysfunction.

CT SCAN

SAH in these aneurysms results in blood in the anterior interhemispheric fissure in essentially all cases, and is associated with intracerebral hematoma in 63% of cases[284]. Intraventricular hematoma is seen in 79% of cases, with the blood entering the ventricles from the intracerebral hematoma in about one third of these. Acute hydrocephalus was present in 25% of patients (late hydrocephalus, a common sequelae of SAH, was not studied).

Frontal lobe infarcts occur in 20%, usually several days following SAH[284]. One of the few causes of the rare finding of bilateral ACA distribution infarcts is vasospasm following hemorrhage from rupture of an ACoA aneurysm. This results in prefrontal lobotomy-like findings of apathy and abulia.

ANGIOGRAPHIC CONSIDERATIONS

Essential to evaluate contralateral carotid, to determine if both ACAs fill the aneurysm. If the aneurysm fills with one side only, it is desirable to inject the other side while cross compressing the side that fills the aneurysm to see if collateral flow is present. Also, determine if either carotid fills both ACAs, or if each ACA fills from the ipsilateral carotid injection (may permit trapping, *see below*).

If additional views are needed to better demonstrate aneurysm

Try oblique 25° away from injection side, center beam 3-4 cm above lateral aspect of ipsilateral orbital rim, orient x-ray tube in Towne's view. A submental vertex view may also visualize the area but the image may be degraded by the amount of interposed bone.

SURGICAL TREATMENT

Approaches

1. pterional approach: the usual approach (*see below*)
2. subfrontal approach: especially useful for aneurysms pointing superiorly when there is a large amount of frontal blood clot (allows clot removal during approach)
3. anterior interhemispheric approach[285]: ✖ contraindicated for anteriorly pointing aneurysms as the dome is approached first and proximal control cannot be obtained (*see below*)
4. transcallosal approach

PTERIONAL APPROACH

Side of craniotomy:

A right pterional craniotomy is used with the following exceptions (for which a left pterional crani is used):

1. large ACoA aneurysm pointing to right: left crani exposes neck before dome
2. dominant left A1 feeder to aneurysm (with no filling from right A1): left crani provides proximal control
3. additional left sided aneurysm

See *Pterional craniotomy* on page 159 for positioning, etc. (use shoulder roll, rotate head 60° from vertical, see *Figure 7-7*, page 159). Craniotomy is as shown in *Figure 7-9*, page 160 (slightly more frontal lobe needs to be exposed than, e.g. for a p-comm aneurysm).

Lumbar drain (if IVC not already inserted) assists with brain relaxation.

MICROSURGICAL DISSECTION

Dissect down sylvian fissure with gentle retraction of frontal lobe away from base of skull. Olfactory nerve visualized first, then optic nerve. Open arachnoid over carotid and optic cistern and drain CSF. Elevate temporal tip, coagulate any bridging temporal tip veins that are present, and expose ICA.

Follow the ICA distally, looking for A1 (exposure of this allows temporary clipping in event of rupture). If the A1 take-off is too high, it may be hidden and would require excessive retraction to expose. Options to increase exposure include

1. gyrus rectus resection: a 1 cm long gyrus rectus cortisectomy is performed[286] just medial to the olfactory tract. Helps find the ipsilateral A1 and often ACoA and A2. This is also helpful for downpointing aneurysms because it permits visualization of the contralateral A1 before

exposing the dome of the aneurysm (for proximal control). May lead to neuropsychiatric deficits. A subpial resection is performed with preservation of the small arterial branch that is consistently located here

2. fronto-temporal-orbital-zygoma removal
3. splitting the sylvian fissure: about 50% of experts do this routinely
4. ventricular drainage

Once found, A1 is followed until the ipsilateral A2 is identified. Then the contralateral A2 is identified and is followed proximally until the contralateral A1 is exposed. The a-comm is usually encountered in the process.

Critical branches to preserve: recurrent artery of Heubner; small ACoA perforators (may be adherent to aneurysm dome). If the aneurysm cannot be clipped, it may be trapped by clipping both ends of the ACoA only if each ACA fills from the carotid on its own side.

Post clipping, some authors recommend fenestrating the lamina terminalis in an effort to reduce the need for post-op shunting.

ANTERIOR INTERHEMISPHERIC APPROACH[285]

Involves minimal brain retraction.

More suitable for an aneurysm that points straight up, but even with this proximal control is poor.

Position: supine with the neck extended ≈ 15°. A transverse skin incision is made in a skin crease in the lower forehead. The authors[285] describe using a 1.5 inch trephine craniotomy in the midline just superior to the glabella. Alternatively, better advantage of the dural opening may be possible with a more rectangular opening. The dural flap is hinged on the superior sagittal sinus. The depth of the aneurysm is ≈ 6 cm from the dura. Proximal control of the A1 branch of the ACA is difficult with this approach.

30.10.2. Distal anterior cerebral artery aneurysms

Aneurysms of the distal anterior cerebral artery **(DACA)** (i.e. the ACA distal to the ACoA) are usually located at the origin of the frontopolar artery, or at the bifurcation of the pericallosal and callosomarginal arteries at the genu of the corpus callosum. Aneurysms located more distally are usually posttraumatic, infectious (mycotic), or due to tumor embolus[287]. DACA aneurysms are often associated with intracerebral hematoma or interhemispheric subdural

hematoma[288] since the subarachnoid space is limited here. Conservative treatment of DACA aneurysms is often associated with poor results. Un-ruptured DACA aneurysms have a higher incidence of bleeding than unruptured aneurysms in other locations. These aneurysms are fragile and adherent to the brain, which predisposes to frequent premature intraoperative rupture.

On arteriography, if both ACAs fill from a single sided carotid injection, it may be difficult to make the important determination as to which ACA feeds the aneurysm. Multiple aneurysms are commonly associated with DACA aneurysms.

TREATMENT

Mycotic aneurysms should be treated as outlined on page 1082.

Aneurysms up to 1 cm from the ACoA may be approached through a standard pterional craniotomy with partial gyrus rectus resection.

Aneurysms > 1 cm distal to the ACoA up to the genu of the corpus callosum, including those of the pericallosal/callosomarginal bifurcation, may be approached surgically by a basal frontal interhemispheric approach[289] via a frontal craniotomy using a bicoronal skin incision. The patient is positioned supine with the neck slightly extended, positioned vertically or just a few degrees to the left. A right sided craniotomy is preferred in most instances (exception: aneurysm dome buried in the right cerebral hemisphere making retraction hazardous), but should cross to the contralateral side by a couple centimeters. It must be taken all the way to the floor of the frontal fossa to permit exposure of the anterior cerebral artery for proximal control. The craniotomy extends ≈ 8 cm above the supraorbital ridge in order to provide leeway in circumnavigating veins bridging to the superior sagittal sinus. The dural flap is based on the superior sagittal sinus. If the sinus needs to be mobilized, it may be divided low anteriorly.

ACA aneurysms distal to the genu of the corpus callosum may also be approached by an interhemispheric approach using a unilateral skin incision. For these, the patient’s neck is not extended, and a parasagittal craniotomy is used that doesn’t need to be as low on the frontal fossa. The cingulate gyri may be difficult to separate, and care must be taken because excessive retraction may pull the cingulate gyrus off the dome of the aneurysm and produce premature rupture.

Ideally, A2 proximal to the aneurysm should be identified initially for proximal control and then followed distally to the aneurysm. When this is not possible, dissection should follow distal ACA branches proximally, towards the

aneurysm, taking care not to disturb the aneurysm. Often, a portion of the cingulate gyrus may need to be removed and sometimes up to 1-2 cm of the anterior corpus callosum may need to be divided.

Surgical complications: Prolonged retraction on the cingulate gyrus may produce akinetic mutism that is usually temporary. The pericallosal arteries are small in caliber and may be atherosclerotic, which together increases the risk of occlusion of the parent artery with the aneurysm clip.

30.10.3. Posterior communicating artery aneurysms

May occur at either end of p-comm; that is at the junction with the PCA, or more commonly at the junction with carotid (typically points laterally, posteriorly, and inferiorly). May impinge on the third nerve in either case and cause third nerve palsy (ptosis, mydriasis, "down and out" deviation) that, is not pupil sparing in 99% of cases.

ANGIOGRAPHIC CONSIDERATIONS

Vertebral artery **(VA)** injection is necessary to help evaluate the p-comm artery:

1. if the p-comm is patent: determine if there is a "fetal circulation" where the posterior circulation is fed only through the p-comm
2. determine if the aneurysm fills from VA injection

If additional views are needed to better demonstrate aneurysm

Try paraorbital oblique 55° away from injection side, center beam 1 cm posterior to inferior portion of lateral rim of ipsilateral orbit, orient x-ray tube 12° cephalad.

See *Pterional craniotomy* on page 159 for positioning, etc.. For the more common aneurysm at the ICA-p-comm junction, rotate head 15-30° from vertical, see *Figure 7-7*, page 159. Craniotomy is as shown in *Figure 7-9*, page 160 (less frontal lobe needs to be exposed than for an ACoA aneurysm).

MICROSURGICAL DISSECTION

Ultimately, the major vector of retraction will be on tip of temporal lobe (less on frontal lobe than in ACoA aneurysm), but the initial approach will be more anterior to reduce risk of intraoperative rupture.

1. dissect down sylvian fissure, retract frontal lobe and come down on optic nerve
2. cautiously elevate temporal tip (aneurysm may be adherent to temporal tip and/or to tentorium), coagulate bridging temporal tip veins if necessary
3. incise arachnoid membrane along the optic nerve from anterior to posterior
4. open arachnoid and drain CSF to gain relaxation
5. start to dissect carotid at anterior margin (at junction with optic nerve) and work towards the posterior margin of carotid where the aneurysm is located (isolating the carotid gives proximal control)

The aneurysm dome usually points laterally, posteriorly and inferiorly, and is encountered before and usually blocks visualization of the p-comm. The aneurysm frequently projects behind the tentorial edge which then obscures the dome.

Critical branches to preserve: anterior choroidal artery, posterior communicating artery (p-comm). If necessary, the p-comm may be sacrificed (e.g. included in clip) without deleterious effect in most cases if there is not a fetal circulation.

30.10.4. Carotid terminus (bifurcation) aneurysms

ANGIOGRAPHIC CONSIDERATIONS

If additional views are needed to better demonstrate aneurysm

Try oblique 25° away from injection side, center beam 3-4 cm above lateral aspect of ipsilateral orbital rim, orient x-ray tube in Towne's view. Also may try submentovertex view.

See *Pterional craniotomy* on page 159 for positioning, etc. (rotate head 30° from vertical, see *Figure 7-7*, page 159). Craniotomy is as shown in *Figure 7-9*, page 160.

30.10.5. Middle cerebral artery (MCA) aneurysms

The following considers MCA aneurysms of the M1-M2 junction

("trifurcation" region, although this is not a true trifurcation, *see page 98*).

SURGICAL TREATMENT

APPROACHES

1. trans-sylvian approach through a pterional craniotomy: the most common
2. superior temporal gyrus approach[290]:
   A. advantages: minimizes brain retraction, possible reduced vasospasm from manipulation of proximal vessels
   B. disadvantages: proximal control difficult, slightly larger bone flap, possible increased risk of seizures

PTERIONAL APPROACH

See *Pterional craniotomy* on page 159 for positioning, etc. (rotate head 45° from vertical, see *Figure 7-7*, page 159).

CRANIOTOMY

Craniotomy is as shown in *Figure 7-9*, page 160. Less frontal lobe needs to be exposed than for, e.g. for an ACoA aneurysm (distance "**B**" in *Figure 7-9* only needs to be ≈ 1 cm). The height "**H**" of the bony opening should be ≈ 5-6 cm (larger than for circle of Willis aneurysms).

MICROSURGICAL DISSECTION

Dissect down sylvian fissure with major vector of retraction on tip of temporal lobe (less on frontal lobe than in ACoA aneurysm). Open arachnoid and drain CSF. Elevate temporal tip, coagulate bridging temporal tip veins, and expose the ICA for proximal control in the event of rupture.

Follow the ICA distally by splitting the sylvian fissure to expose the M1 (again, for proximal control). Although exposure for proximal control is helpful to have as a contingency, one may be able to avoid temporary clipping of the MCA in the event of intraoperative rupture by controlling bleeding with a large suction, and subsequent clip placement (since the blood flow through the MCA is not as voluminous as through the ICA, and the surgical access to these aneurysms is usually fairly unrestricted).

Critical branches to preserve: distal MCA branches, recurrent perforators from the origin of the major MCA branches.

30.10.6. Supraclinoid aneurysms[291]

Applied anatomy

The carotid artery exits the cavernous sinus and enters the subarachnoid space at the dural constriction known as the **carotid ring** (AKA clinoidal ring). The supraclinoid portion of the carotid artery may be divided into the following segments[292]:

1. **ophthalmic segment**: the largest portion of the supraclinoid ICA. Lies between the take-off of the ophthalmic artery and the posterior communicating artery (PCoA) origin. The proximal portion of this (including the origin of the ophthalmic artery) is often obscured by the anterior clinoid process. Branches include:
   A. ophthalmic artery: usually originates from the supracavernous ICA just after the ICA enters the subarachnoid space (*see page 99* for variants). Enters the optic canal positioned inferolateral to the optic nerve
   B. superior hypophyseal artery: the largest of several perforators supplying the dura of the cavernous sinus and the superior pituitary gland and stalk
2. communicating segment: from the PCoA origin to the origin of the anterior choroidal artery (AChA)
3. choroidal segment: from AChA origin to the terminal bifurcation of the ICA

30.10.6.1. Ophthalmic segment aneurysms[293]

Ophthalmic segment aneurysms **(OSAs)** include (NB: nomenclature varies among authors):

1. ophthalmic artery aneurysms:
2. superior hypophyseal artery aneurysms:
   A. paraclinoid variant: usually does not produce visual symptoms
   B. suprasellar variant: when giant, may mimic pituitary tumor on CT

PRESENTATION *(EXCLUDING INCIDENTAL DISCOVERY)*

OPHTHALMIC ARTERY ANEURYSMS

Arise from the ICA just distal to the origin of ophthalmic artery. They project dorsally or dorsomedially towards the lateral portion of the optic nerve.

Presentation:
- ≈ 45% present as SAH
- ≈ 45% present as visual field defect:
  A. as the aneurysm enlarges it impinges on the lateral portion of the optic nerve → inferior temporal fiber compression → ipsilateral monocular superior nasal quadrantanopsia
  B. continued enlargement → upward displacement of the nerve against the **falciform ligament** (or fold) → superior temporal fiber compression → monocular inferior nasal quadrantanopsia
  C. in addition to near-complete loss of vision in the involved eye, compression of the optic nerve near the chiasm may produce a superior temporal quadrant defect in the contralateral eye (**junctional scotoma** AKA "pie in the sky" defect) from injury to the **anterior knee of Wilbrand** (nasal retinal fibers that course anteriorly for a short distance after they decussate in the contralateral optic nerve[294])
- ≈ 10% present as both

SUPERIOR HYPOPHYSEAL ARTERY ANEURYSMS

Originate in the small subarachnoid pocket medial to the ICA near the lateral aspect of the sella. The direction of enlargement is dictated by the size of this pocket and the height of the lateral sellar wall, resulting in two variants: paraclinoid & suprasellar.

Suprasellar variant may actually grow to a size large enough to compress the pituitary stalk and cause hypopituitarism and "classic" chiasmal visual symptoms (bilateral temporal hemianopsia).

ANGIOGRAPHIC CONSIDERATIONS

A notch can often be observed in the in the anterior, superior, medial aspect of giant ophthalmic artery aneurysms due to the optic nerve[295].

If additional views are needed to better demonstrate aneurysm

Try oblique 25° away from injection side, center beam 3-4 cm above lateral aspect of ipsilateral orbital rim, orient x-ray tube in Towne's view. Try

submentovertex view.

SURGICAL TREATMENT[291]

OPHTHALMIC ARTERY ANEURYSMS

If necessary, the ophthalmic artery may be sacrificed without worsening of vision in the vast majority. Clipping a contralateral ophthalmic artery aneurysm is not technically difficult, and is not uncommonly required as OSAs are often multiple.

The aneurysm arises from the superomedial aspect of the ICA just distal to the ophthalmic artery origin, and projects superiorly.

Cutting the falciform fold early decompresses the nerve, and helps minimize worsening of visual deficit from surgical manipulation.

For unruptured aneurysms, drill off anterior clinoid via an extradural approach before opening dura to approach neck; for ruptured aneurysms, this may not be as safe.

In most cases, a side-angled clip can be placed parallel to the parent artery along the neck of the aneurysm.

SUPERIOR HYPOPHYSEAL ARTERY ANEURYSMS

If necessary, the superior hypophyseal artery on one side may be clipped without demonstrable deleterious effect (due to bilateral supply to stalk and pituitary). Clipping a contralateral superior hypophyseal aneurysms is not really feasible.

With a usual pterional approach, the carotid artery is usually encountered first, and with large aneurysms is usually bowed laterally towards the surgeon. Clinoidal removal is usually required. The entire ICA wall may appear to be involved, and it may necessitate temporary ICA clipping (with cerebral protection) to reconstitute the ICA using encircling clips parallel to the parent vessel.

30.10.7. Posterior circulation aneurysms

(See page 1074 for *basilar tip* aneurysms). Clinical syndrome of SAH in the posterior fossa is indistinguishable from that due to anterior circulation aneurysms except for possible increased tendency towards respiratory arrest and subsequent neurogenic pulmonary edema[296]. Vasospasm following posterior

fossa SAH may be more likely to cause midbrain symptoms than vasospasm due to SAH elsewhere.

HYDROCEPHALUS

In Yamaura's series[297], 12% of patients required external ventricular drainage **(EVD)** following posterior fossa SAH to remove bloody CSF causing hydrocephalus, and 20% eventually required permanent ventricular shunt.

30.10.7.1. Vertebral artery aneurysms

Traumatic vertebral artery aneurysms **(VAA)** (AKA dissecting aneurysms) are more common than non-traumatic VAAs. The following discussion concerns non-traumatic VAA.

Most VAAs arise at the VA-PICA junction. Other sites: VA-AICA, VA-BA.

ANGIOGRAPHIC CONSIDERATIONS

Angiography of VAA should assess the contralateral VA for patency in case of the need to trap the aneurysm. **Allcock test** (vertebral artery injection with carotid compression) may be used to assess patency of circle of Willis. Test occlusion with a balloon catheter can determine if patient will tolerate occlusion (a double lumen balloon will even allow measurement of distal back pressure).

PICA ANEURYSMS

For PICA anatomy, see *Figure 5-20*, page 102. For arteriogram, see *Figure 5-21*, page 103.

Comprise ≈ 3% of cerebral aneurysms. 3 common sites:

1. VA at the VA-PICA junction[209]:
    A. saccular aneurysms: most commonly at the distal (superior) angle. An aneurysm in this location should be suspected with a CT showing blood predominantly in the 4th ventricle[218] (aneurysmal dome may adhere to foramen of Luschka; rupture fills the ventricles with little subarachnoid blood visible on CT). The level is as varied as the PICA origin, and ranges from as low as the foramen magnum to as high as the pontomedullary junction. Most VA-PICA aneurysms lie in the anterolateral portion of the medullary cistern[298], anterior to the first dentate ligament[299]. However, the PICA origin may sometimes lie in the midline or across it

   B. fusiform aneurysms: usually the result of prior arterial dissection: *see page 1163*
2. PICA aneurysms distal to the VA-PICA junction: tend to be fragile and often develop multiple hemorrhages in a relatively short period, ∴ should be treated promptly, even when discovered incidentally
3. fusiform VA aneurysms involving PICA

ANGIOGRAPHIC CONSIDERATIONS

If additional views are needed to better demonstrate aneurysm

Try paraorbital oblique 55° away from injection side, center beam on foramen magnum, orient x-ray tube 12° cephalad.

TREATMENT

Options:

1. direct aneurysmal clipping is the preferred treatment
2. endovascular coil embolization: not as effective as clipping for relief of symptoms due to brainstem or cranial nerve compression
3. choices for unclippable and uncoilable aneurysms (e.g. fusiform, giant, or dissecting aneurysms) include:
   A. proximal (hunterian) VA ligation[300] which must be distal to the PICA origin to prevent severe morbidity or mortality[301]
   B. occlusion of the VA distal to the PICA origin (usually done endovascularly)
   C. midcervical VA occlusion (allows collateral flow through suboccipital muscular branches) e.g. endovascular Amplatzer plug

One approach to the VA-PICA junction is via a low extreme-lateral p-fossa approach. However, if the aneurysm is too far anterior to the brain stem, it may be totally out of vision or reach. Also, since these aneurysms usually project posteriorly and superiorly, the critical PICA will be directly in harms' way. Direct lateral approach more directly exposes the aneurysm[302] through a lateral suboccipital transcondylar approach.

Position: options include sitting position (less frequently used, see *Sitting position*, page 153) or lateral oblique ("park bench").

Lateral oblique position

Position: side of involved PICA is up, thorax elevated ≈ 15°. Head inline with the thorax, neck slightly flexed, and slightly rotated 20° toward the floor (away from the side of the aneurysm). Upper shoulder depressed with adhesive tape. Lumbar spinal subarachnoid catheter placed, allows CSF drainage once dura is opened.

Options for skin incision:

Avoid opening too far laterally, otherwise the muscle mass impedes vision[303] (p 1747).

1. paramedian vertical incision } from just above superior nuchal line to C2 vertebra[298]
2. midline vertical incision (hockey stick) } from just above superior nuchal line to C2 vertebra[298]
3. “sigmoid” incision starting 2 cm medial to mastoid notch, and curving to midline at level of C1 arch[304]

Craniectomy: lateral exposure of bone to the base of the mastoid, medially crossing the midline. Need not be quite as high as the transverse sinus. The foramen magnum is removed to its lateral margin. Removing the posterior arch of C1 from midline to the sulcus arteriosus (under VA) may help with proximal VA exposure[304] but is not usually necessary[305].

Dural opening: K-shaped dural opening with a linear incision across the band at the foramen magnum (some patients have a sinus known as the arcuate sinus here that may require vascular clips).

Approach: first, gain proximal control of the VA where it first becomes intradural (in case of aneurysmal rupture). Retract cerebellum superiorly (caution: aneurysm dome may be adherent). Follow VA up from point where it enters dura; PICA origin then encountered usually just at neck of aneurysm (PICA origin may be confused for continuation of VA). Dissection must spare branches of pharyngeal filaments of spinal accessory nerve and lower filaments of vagus. May place temporary clip on VA proximal to PICA. Permanent clip usually placed between the fibers of IX & X above and XI below. It is better to leave a small residual aneurysm than to risk compromising PICA[305].

Postoperative care: when neuropraxia of the lower cranial nerves is likely (in cases of difficult dissection or traction applied during clipping) the patient is kept intubated overnight. Patients who do not tolerate extubation at this point are

immediately reintubated and elective tracheostomy is scheduled. Tracheostomy is maintained until the neuropraxia resolves.

30.10.7.2. Vertebrobasilar junction aneurysms

Saccular aneurysms located where the two vertebral arteries join often form at the location of a basilar artery fenestration (basilar fenestration aneurysm).

Angiographic considerations

If additional views are needed to better demonstrate aneurysm

Try oblique 15° away from injection side, center beam on foramen magnum, orient x-ray tube 25° Towne. Try submentovertex view.

CT-angiogram may be helpful as an adjunct because it can opacify both vertebral arteries simultaneously (not generally feasible with catheter angiogram).

Surgical approaches

1. suboccipital approach: for most; performed in lateral oblique position
2. subtemporal-transtentorial approach if the vertebrobasilar junction is high; performed in supine position

Suboccipital approach in lateral oblique position

NB: the side of approach must be chosen based on angiogram, as the extreme tortuosity of the VAs may cause the aneurysm of one VA to lie on the contralateral side of the brain stem.

Position: thorax elevated ≈ 15°. Head inline with the thorax, neck slightly flexed, and slightly rotated away from side of aneurysm. Upper shoulder depressed with adhesive tape. Spinal drain placed for CSF drainage, opened only once dura is opened.

30.10.7.3. AICA aneurysms

Angiographic considerations

If additional views are needed to better demonstrate aneurysm

Try AP or submentovertex view, center beam on nasion, orient x-ray tube 15° caudad.

30.10.8. Basilar bifurcation aneurysms

AKA **basilar tip aneurysms**. The most common posterior circulation aneurysm. Comprise ≈ 5% of intracranial aneurysms.

Presentation

Most present with SAH indistinguishable from SAH due to anterior circulation aneurysmal rupture. Enlargement of the aneurysm prior to rupture may rarely compress the optic chiasm → bitemporal field cut (mimicking pituitary tumor), or occasionally may compress the third nerve as it exits from the interpeduncular fossa → oculomotor nerve palsy[296].

CT/MRI scan

May occasionally be seen on CT or MRI as round mass in region of suprasellar cistern. With SAH, tend to see blood in interpeduncular cistern with some reflux into 4th (and to a lesser extent, third and lateral) ventricle. Occasionally may mimic pretruncal nonaneurysmal SAH (*see page 1085*).

Angiography

Dome usually points superiorly. Should evaluate flow through posterior communicating arteries (may require Allcock test) in case trapping is required. Need to assess the height of the basilar bifurcation in relation to the dorsum sella (see *Approaches* below).

If additional views are needed to better demonstrate aneurysm

Try oblique 25° away from or towards injection side, center beam 3-4 cm above lateral aspect of ipsilateral superior orbital rim, orient x-ray tube 25° Towne. Try submentovertex view.

Critical angiographic features to assess: On angiogram or CTA:

1. general features: *see page 1039*
2. orientation: determines whether surgery is an option. Posteriorly pointing aneurysms obscure perforators which may be adherent to the aneurysm, making surgery more difficult
3. patency of PCAs & SCAs
4. patency and size of p-comms
   A. diameter of p-comm > 1 mm is needed to support collateral flow (expert opinion)
   B. to determine if the P1's can be sacrificed
   C. P-comm patency and size is important for endovascular treatment as a potential route for deployment of horizontally oriented stent extending from P1 to contralateral P1306, 307
   D. which can facilitate temporary clipping, or sacrifice, or placement of stents.
5. height of the aneurysm relative to the posterior clinoid process which will affect the selection of surgical approach[308, 309] (the range of height of the posterior clinoid is 4-14 mm[309])
   A. supraclinoidal: aneurysm neck > 5 mm superior to posterior clinoid process
   B. clinoidal: aneurysm neck within 5 mm of posterior clinoid process
   C. infraclinoidal: aneurysm neck > 5 mm inferior to posterior clinoid process

SURGICAL TREATMENT

TIMING

Initial experience tended to favor allowing basilar tip aneurysms to "cool-down" for ≈ 10-14 days after SAH before attempting surgery to permit cerebral edema to subside. More recently, early surgery for these aneurysms has been advocated as for anterior circulation aneurysms[310] (see *Timing of aneurysm surgery*, page 1060). However, some surgeons still recommend waiting ≈ 1 week[311], and most would agree that if there are obvious technical difficulties because of size, configuration or location of the aneurysm, that early surgery may not be appropriate. Also, if during the craniotomy it becomes apparent that cerebral edema is impairing the exposure, the operation should be aborted and attempted again at a later date.

APPROACHES

1. right subtemporal craniotomy (classical approach of Drake): approached through the incisura or division of the tentorium. Most basilar tip aneurysms are probably best approached via pterional approach (*see below*) except for posteriorly pointing aneurysms
   A. advantage:
      1. less distance to basilar tip
      2. may be better than pterional approach for aneurysms projecting posteriorly or posteroinferiorly[311]
   B. disadvantages:
      1. requires temporal lobe retraction (minimized with lumbar drainage, mannitol, and possibly zygomatic arch section[312])
      2. poor visualization of contralateral P1 segment and thalamoperforators
2. pterional approach (described by Yasargil): trans-Sylvian (*see below*)
   A. advantages:
      1. little or no retraction on temporal lobe (unlike subtemporal approach)
      2. better visualization of both P1 segments and thalamoperforators
      3. other aneurysms, e.g. of the anterior circulation, can be dealt with at the same sitting
   B. disadvantages:
      1. increases reach to aneurysm by ≈ 1 cm compared to subtemporal
      2. requires wide splitting of the sylvian fissure
      3. operating field is narrower than subtemporal approach
      4. perforators arising from the posterior aspect of P1 may not be visible
3. modified pterional craniotomy: may allow trans-sylvian *or* subtemporal approach[311]. The craniotomy is taken further posteriorly than a standard pterional craniotomy
4. orbitozygomatic approach: allows access to portions of the basilar artery below the bifurcation. May be augmented by removal of the top of the clivus

Optional resection of the temporal tip will increase exposure of either approach. Unlike most anterior circulation aneurysms, securing proximal control is very difficult.

If the basilar bifurcation is high above the dorsum sella, then more retraction is required on a subtemporal approach than for a normal bifurcation height (near the dorsum sella). A high bifurcation is dealt with on a trans-sylvian approach by opening the sylvian fissure more widely, or by a subfrontal approach through the third ventricle via the lamina terminalis[313]. A low bifurcation may require splitting the tentorium behind the 4th nerve.

PTERIONAL APPROACH[314]

Risks include: oculomotor palsy in ≈ 30% (most are minimal and temporary).

Approach is from the right unless:

1. additional left sided aneurysm (e.g. p-comm aneurysm) which could be treated simultaneously by a left sided approach
2. aneurysm points to the right
3. aneurysm is located to the left of midline (the operation is more difficult when the aneurysm is even just 2-3 mm contralateral to the craniotomy)[311]
4. patient has right hemiparesis or left oculomotor palsy

See *Pterional craniotomy* on page 159 for general information. Rotate the head ≈ 30° off the vertical so that the malar eminence points directly upward (see *Figure 7-7*, page 159). Slight neck flexion is used for low-lying aneurysms, slight extension for high ones. Craniotomy is as shown in *Figure 7-9*, page 160, with aggressive removal of the sphenoid wing. The sphenoid wing and the orbital roof may be reduced with a drill. The posterior clinoid can be removed to improve exposure.

Approach

The sylvian fissure is split until the take-off of the proximal M1 from the carotid terminus is identified. The approach is medial to the ICA (between the ICA and optic nerve) when this space is ≥ 5-10 mm. If the ICA is close to the optic nerve, an approach lateral to the ICA may be used, aided by medial retraction of the ICA/M1 segment (see *Figure 7-10*, page 161). Here, the exposure is limited by the height of the M1 branch above the skull base, and if the basilar tip height above the skull base greatly exceeds this, clipping via this approach is not feasible[297].

The 3rd nerve is identified. Also the p-comm and the anterior choroidal artery **(AChA)** are located as they arise from the posterior surface of the ICA (to

differentiate between them: the p-comm origin is proximal to that of the AChA, p-comm courses perpendicular to Liliequist's membrane whereas AChA courses obliquely into the crural cistern). The p-comm is followed posteriorly through Liliequist's membrane which is opened revealing the prepontine cistern. The p-comm is followed until it joins the PCA at the P1/P2 junction. If p-comm is absent, follow the third nerve back to find where it emerges between PCA and SCA. P1 is followed proximally to the basilar bifurcation region where the contralateral P1 and both SCAs are identified. Caudal dissection of Liliequist's membrane exposes the interpeduncular cistern with proximal BA (this exposure is critical for proximal control of BA in the event of aneurysmal rupture).

Thalamoperforating arteries (ThPAs) arise from the distal p-comm and proximal PCA, and often compromise the access. Early poor results with clipping of basilar tip aneurysms has been attributed to sacrificing these vessels, which produces lacunar infarcts in the thalamus, midbrain, subthalamic, and pretectal regions. If hypoplastic, the p-comm may be divided between clips to improve exposure (preserving the ThPAs which will then arise from the stumps). Similarly, a hypoplastic P1 may be divided if the PCA fills from the p-comm. If the ThPAs make it impossible to clip the aneurysm, some may have to be sacrificed, which is best done at their origin. Fortunately, there are some anastomoses[315] and thus they are not entirely end-arteries as originally thought.

OUTCOME

If the aneurysm is not giant, then these may be as safe to clip as anterior circulation aneurysms. Overall mortality is 5%, and morbidity is 12% (mostly due to injury to perforating vessels)[23].

30.10.9. Basilar trunk aneurysms

Most aneurysms of the basilar trunk are fusiform in morphology. Surgical access for these is extremely difficult.

30.11. Post-op orders for aneurysm clipping

1. admit PACU, transfer to ICU (neuro unit if available) when stable
2. VS: q 15 min x 4 hrs, then q 1 hr. Temperature q 4 hrs x 3 d, then q 8 hrs.

Neuro check q 1 hr

3. activity: bed rest (BR) with HOB elevated 20-30°
4. knee high TED hose and pneumatic compression boots
5. I & O q 1 hr (if no Foley: straight cath q 4 hrs PRN bladder distension)
6. incentive spirometry q 2 hrs while awake (do not use following transsphenoidal surgery)
7. IVF: NS + 20 mEq KCl/L @ 90 ml/hr

For extubated patients

8. diet: NPO except minimal ice chips and meds as ordered
9. O_2: 2 L per NC

For intubated patients

8. diet: NPO. NG tube to intermittent suction. May clamp for 1 hour after meds given
9. ventilator orders

For all patients

10. meds:
    A. H_2 antagonist, e.g. ranitidine 50 mg IVPB q 8 hrs
    B. Keppra® (levetiracetam): 500 mg PO or IV q 12 hours. Maintain therapeutic AED levels for 2-3 months post-op for most supratentorial craniotomies
    C. Cardene® drip: titrate to keep SBP < 160 mm Hg and/or DBP < 100 mm Hg (use cuff pressures, may use A-line pressures if they correlate with cuff pressures)
    D. analgesics: fentanyl (unlike morphine, does not cause histamine release. Lowers ICP) 25-100 mcg (0.5-2 ml) IVP, q 1-2 hrs PRN
    E. acetaminophen (Tylenol®) 650 mg PO/PR q 4 hrs PRN temperature > 100.5° F (38 C)
    F. mini-dose heparin or enoxaparin {for DVT prophylaxis (no difference in heparin-induced thrombocytopenia with these 2 agents[316])}
    G. calcium channel blockers (see admitting orders *page 1042*): nimodipine (Nimotop®) 60 mg PO/NG q 4 hrs or 30 mg q 2 hrs to avoid dips in BP. May be given IV where available
    H. *continue prophylactic antibiotics if used:* (e.g. cefazolin (Kefzol®) 500-1000 mg IVPB q 6 hrs x 24 hrs, then D/C)
11. if available, transcranial doppler to monitor MCA, ACA, ICA, VA and BA

velocities and Lindegaard ratio (*see page 1048*) {typical protocol is 3 **x** per week)

12. labs:
    A. CBC once stabilized in ICU and q d thereafter
    B. renal profile once stabilized in ICU and q 12 hrs thereafter
    C. ABG once stabilized in ICU and q 12 hrs x 2 days, then D/C (also check ABG after any ventilator change if patient on ventilator)
13. call M.D. if any deterioration in crani checks, for T > 101° (38.5 C), sudden increase in SBP, SBP < 120, U.O. < 60 ml/2-hrs

30.12. Unruptured aneurysms

Unruptured intracranial aneurysms **(UIA)** includes **incidental aneurysms** (those that do not produce any symptoms and are discovered incidentally) and aneurysms that produce symptoms other than those due to hemorrhage (e.g. pupillary dilatation due to third nerve compression). UIA merit consideration for treatment since the outcome from SAH with or without surgery is poor even under the best of circumstances. About 65% of patients die from the first SAH[317], and even in patients with no neurologic deficit after aneurysm rupture, only 46% fully recover, and only 44% return to their former jobs[1]. Estimated prevalence of incidental aneurysms is 5-10% of the population[1].

Presentation

See items other than "rupture" in *Presentation of aneurysms*, page 1055.

Natural history

Risk of bleeding from UIA differs from aneurysms that have ruptured. True risk is not known with certainty. The largest, most detailed study to date is the ISUIA[318].

> Σ There appears to be 2 distinct types of aneurysms: those that rupture, and those that tend to remain stable. Most UIAs seen in the clinic fall into the latter group

Spontaneous thrombosis of unruptured aneurysms may occur rarely (*see page 1058*).

The natural history and treatment results are influenced by[319] (see *Surgical outcome* below):

1. patient factors:
   A. history of previous SAH from a separate aneurysm[318] significantly increases the risk of rupture of an UIA
   B. patient age
   C. concurrent medical conditions
2. aneurysm characteristics[318]
   A. aneurysm size: the most important predictor for future rupture (*see below*) except (for unknown reasons) in patients with prior SAH from another source
   B. location: p-comm, vertebrobasilar/posterior cerebral, and basilar tip UIAs were more likely to rupture
   C. morphology
3. surgical capabilities
   A. experience of the surgical team
   B. possibly by ancillary services available

An estimate for UIA is ≈ **1% per year**. The risk of bleeding in patients with multiple aneurysms was higher (6.8%) than for patients with single aneurysms (2.3%)[320].

Aneurysm size: Risk of rupture appears critically dependent on aneurysm diameter[321]. Estimated annual risk of rupture of aneurysms of diameter **< 10 mm** is **0.05%** (range: 0-4%)[208, 318A] and is lower than for diameters **≥ 10 mm** which is **1%** (range: 0.46-1.54%)[318, 322] (this seems paradoxical since the mean diameter of aneurysms on post-rupture angiograms is 7.5 mm; this may be due to a shrinkage of aneurysms following rupture). The rupture rate was 6% in the first year with giant (≥ 2.5 cm) UIAs. Furthermore, aneurysms are <u>not</u> static, and have been shown to increase in size on serial angiograms[323].

A. selection bias may play a role in lowering the apparent SAH rate as follows: enlarging aneurysms (which have increased risk of rupture) may produce symptoms and may be preferentially referred for surgery, and the inclusion of cavernous carotid aneurysms (which rarely cause SAH)

SURGICAL OUTCOME

There are no prospective randomized studies of treatment natural history vs. treatment options[319], and most data are either from personal series or are retrospective. Summary of 260 patients show no surgical mortality, and morbidity of 0-10.3% (6.5% major and 8% minor morbidity in the multicenter study)[1]. A recent study found surgical mortality of 2.3% at 30-days, and 3.8% at 1 year[318]. A meta-analysis found 2.6% case fatality[324].

Operative morbidity was mild in 5%, moderate to severe in 6%[324]. Morbidity also increased with aneurysm size (2.3% for diameter < 5 mm, 6.8% for 6-15 mm, and 14% for 16-25 mm)[318]. Morbidity also varied with location (4.8% for p-comm, 8.1% for MCA, 11.8% for ophthalmic, 15.5% for anterior communicating, and 16.8% for carotid bifurcation). Morbidity also increases with patient age (6.5% for age < 45 yrs, 14% for age 45-64, and 32% for age > 64)[318].

MANAGEMENT

To understand the calculation of *cumulative* risk for aneurysmal rupture, *see page 1100* for a discussion of this issue related to AVMs which also pertains to aneurysms.

Decision analysis

Requires data about the natural history (*see above*), life expectancy, and morbidity and mortality of SAH and aneurysm surgery.

In one such study[325], using the values shown in *Table 30-13*, the result obtained was that a life expectancy of 12 more years is the break-even point, i.e. if the patient is not expected to live for 12 more years, then non-surgical management is a better choice than surgery (this result involves numerous assumptions and estimations; e.g. 5% “risk aversiveness” (intermediate) relates to patient’s fears of immediate surgical risk vs. risk of rupture spread over many years). Another analysis of various scenarios for a 50 year old female found that treatment was cost effective for UIAs that were symptomatic, ≥ 10 mm diameter, or with a previous history of SAH[326].

Table 30-13 Data used in decision analysis of management of unruptured aneurysms[325]

	Typical value	Range
annual risk of rupture*	1%	0.5-2%
3 month mortality of SAH	55%	50-60%

serious morbidity after SAH	15%	10-20%
surgical morbidity & mortality	2% & 6%	4-10%

* this is an intermediate risk for aneurysms 6-10 mm diameter (NB: size may change; small aneurysms may grow)

Management recommendations based on aneurysm size

Numerous recommendations have been made for a critical size above which an un-ruptured aneurysm should be considered for surgery, and have included 3 mm[322, 5] mm[327, 7] mm[328], and 9 mm[208]. And again, the patient's expected longevity must be taken into account. One proposal is to promptly treat unruptured aneurysms ≥ 10 mm, to repair those measuring 7-9 mm in young and middle-aged patients, and to follow smaller aneurysms with serial angiography[329].

Summary of the American Heart Association Stroke Council recommendations

Table 30-14 summarizes factors favoring treatment made based on a review of the literature[319] (only level IV and V evidence was found, and therefore only grade C recommendations can be made (i.e. an array of potential actions, any of which could be considered appropriate)[330, 331]). Patients for whom expectant management is elected should have periodic CT, MRA or selective contrast angiography seeking changes in aneurysm size or configuration. Symptomatic large or giant aneurysms carry increased risk of treatment.

In all treatment decisions, coexisting medical conditions must be taken into account.

Table 30-14 Factors favoring treatment of UIAs

Factor	Features favoring treatment
patient age	young age (risk of SAH accumulates with time)
previous SAH	UIA in patient with previous SAH due to another aneurysm
aneurysm location	basilar apex
aneurysm size	small UIAs approaching 10 mm in size, and in particular UIAs ≥ 10 mm size
aneurysm configuration	UIAs with daughter aneurysm or other unique hemo-dynamic featrures

family history	family members with aneurysms or aneurysmal SAH
symptomatic aneurysms	development of new symptoms related to mass effect may indicate enlargment and urgent treatment is recommended
changes on follow-up studies	enlargment or change in configuration

Recommended follow-up for UIAs

Σ Annual follow-up TOF-MRAs are recommended for most incidental aneurysms that are not treated. Intervention is indicated for any documented growth.

Background: The morbidity from catheter arteriograms is probably too high to recommend them for this purpose. CTA is more accurate than MRA, but involves iodine contrast and radiation. A TOF-MRA (not gadolinium-MRA) has no known risks and does not involve radiation.

Unfortunately, most aneurysms rupture without demonstrable enlargement on follow-up. Aneurysms do not grow at a constant rate, and it may take several years to appreciate a millimeter of increased size on MRA. Over a 47 month median follow-up, only 10% of aneurysms enlarged on follow-up MRA[332]. Larger aneurysms (≥ 8 mm original diameter) more frequently showed growth[332]. An aneurysm showing any growth should be treated (it is not really known if enlargement is associated with increased risk of rupture, but there are probably few situations like this where the physician would be willing to wait and see).

Unruptured cavernous carotid artery aneurysms

Most cavernous carotid artery aneurysms **(CCAAs)** develop on the horizontal segment of the artery.

Presentation:

1. CCAAs may be discovered incidentally
   A. on arteriography for other reason
   B. on MRI
   C. occasionally on CT
2. when symptomatic:
   A. usually present with:
      1. headache
      2. cavernous sinus syndrome (*see page 1204*): primarily produces

diplopia (due to ophthalmoplegia). Classically the third nerve palsy from enlarging CCAA will not produce a dilated pupil because the sympathetics which dilate the pupil are also paralyzed[85 (p 1492)]
3. those that expand through the carotid ring into the subarachnoid space may cause monocular blindness[291]

B. rarely, pain (retro-orbital or pain mimicking trigeminal neuralgia[220, 221]) or a carotid-cavernous fistula **(CCF)** are the sole manifestation
C. when CCAAs rupture, they usually produce a CCF
D. life threatening complications are rare, but may be more common with *giant* intracavernous aneurysms[333]. Manifestations include:
   1. SAH[333, 334] } especially CCAAs that straddle the carotid ring[A]
   2. arterial epistaxis from rupture into sphenoid sinus (usually with traumatic aneurysms, *see page 1081*) } especially CCAAs that straddle the carotid ring[A]
   3. emboli

A. subarachnoid extension of CCAAs may be indicated by "waisting" of the aneurysm on angiography[336]

Indications for treatment:

1. unruptured CCAAs: the natural history is not precisely known
   A. symptomatic: patients with intolerable pain or visual problems[335]
   B. giant aneurysms: especially those that straddle the clinoidal ring[A]
   C. aneurysms that enlarge on serial imaging
   D. controversial: incidental aneurysms in the distribution of a stenotic carotid artery for which carotid endarterectomy is indicated. There has been no evidence that doing the endarterectomy increases the risk of rupture, and, as indicated above, most ruptures are not life threatening and so the carotid disease should be treated according to it's own merits
2. ruptured CCAAs:
   A. emergent treatment for cases with epistaxis or SAH
   B. urgent treatment for CCFs with severe eye pain or threat to vision

Treatment options for CCAAs:

Treatment of small incidental intracavernous CCAAs is not generally

indicated[319].

For other unruptured CCAAs, options include detachable coils in an attempt to thrombose the aneurysm (*see page 1058*). This results in reduction of mass effect in ≈ 50%. Open surgical treatment is rarely appropriate. Aneurysms that rupture and produce a carotid-cavernous fistula may be treated by endovascular occlusion (*see page 1113*).

30.13. Multiple aneurysms

Multiple aneurysms are present in 15-33.5% of cases of SAH[1]. In one study of multiple factors, hypertension was found to be the most important one associated with multiplicity[337].

When a patient presents with SAH and is found to have multiple aneurysms, the following may be clues as to which aneurysm has bled:

1. epicenter (center of greatest concentration) of blood on CT or MRI[53, 56]
2. area of focal vasospasm on angiogram
3. irregularities in the shape of the aneurysm (so-called "Murphy's tit")
4. if none of the above help, then suspect the largest aneurysm
5. NB: in one series, the most common cause of post-op bleeding in 93 patients with multiple aneurysms was felt to be from rebleeding of the original aneurysm that ruptured that was actually missed on initial angiogram[338]

30.14. Familial aneurysms

The role of inheritance in the development of intracranial aneurysms **(IA)** is well established for disorders such as polycystic kidney disease, and connective tissue disorders such as Ehlers-Danlos type IV, Marfan syndrome, and pseudoxanthoma elasticum (see *Conditions associated with aneurysms*, page 1057).

Additional cases of IAs in identical twins[339, 340] as well as familial aggregations of IAs without a recognized inherited disorder have also been reported but are felt to be rare (it has been estimated that < 2% of IAs are

familial[341]). Most reported cases consist of only 2 family members with IAs, and these are most commonly siblings[342]. Analysis of case reports reveals that when IAs occur in siblings they tend to occur at identical or mirror image sites, and in comparison to sporadic IAs, familial IAs tend to rupture at a smaller size and at a younger age, and that the incidence of anterior communicating artery aneurysms is lower[343]. It has been postulated that IAs occurring in siblings may represent a distinct population of IAs[344].

The indications and best method for investigation of asymptomatic relatives of a patient found to harbor an intracranial aneurysm are controversial. Negative studies (angiography, DSA, MRA…) do not guarantee that at a later date an aneurysm will not be discovered that either subsequently developed or expanded, or was simply not detected on the initial study[345-347]. Cerebral angiography is the most sensitive study, however, the risk and expense may not justify its use as a screening test in many cases. Furthermore, there is some evidence that aneurysms that rupture tend to do so shortly after their formation[208] which would reduce the value of screening.

Screening recommendations: first-degree relatives (especially siblings) are at higher risk of harboring IAs[348] and should undergo MRI and MRA screening. Findings suspicious for IA(s) require follow-up with four vessel arteriography to confirm suspected lesions (MRA has a high false-positive rate of ≈ 16%[58]) and to rule-out additional IAs.

30.15. Traumatic aneurysms

Traumatic aneurysms **(TAs)** comprise < 1% of intracranial aneurysms[349, 350]. Most are actually false aneurysms, AKA pseudoaneurysms (a rupture of all the vessel wall layers with the "wall" of the aneurysm being formed by surrounding cerebral structures[351]). They may occur rarely in childhood. The mechanism of injury usually falls into one of the following groups[352]:

1. those arising from penetrating trauma: usually from gunshot wounds, although penetration with a sharp object (which is less common) may be more prone to cause traumatic aneurysms[353]
2. those arising from closed head injury: more common. Theories of pathogenesis include traction injury to the vessel wall or entrapment within a fracture. Tend to occur either:

A. peripherally
   1. distal anterior cerebral artery aneurysms: secondary to impact against the falcine edge
   2. distal cortical artery aneurysms: often associated with an overlying skull fracture, sometimes a growing skull fracture

B. at the skull base, usually involving the ICA in one of the following sites:
   1. petrous portion } virtually always associated with basal skull fractures
   2. cavernous carotid artery: } virtually always associated with basal skull fractures
      a. aneurysm enlargement may cause a progressive cavernous sinus syndrome } virtually always associated with basal skull fractures
      b. rupture may lead to a posttraumatic carotid-cavernous fistula (*see page 1113*) or to massive epistaxis in the presence of a sphenoid sinus fracture[354-356] } virtually always associated with basal skull fractures
   3. supraclinoid carotid artery

3. iatrogenic: following surgery in or around the skull base, the sinuses, or orbits (including following transsphenoidal surgery[357])

Presentation

1. delayed intracranial hemorrhage (subdural, subarachnoid, intraventricular, or intraparenchymal): the most common presentation. TAs tend to have a high rate of rupture
2. recurrent epistaxis
3. progressive cranial nerve palsy
4. enlarging skull fracture
5. may be incidental finding on CT scan
6. severe headache

Treatment

Although there are case reports of spontaneous resolution, treatment is usually recommended. ICA aneurysms at the skull base should undergo trapping or endovascular embolization. Peripheral lesions should be treated surgically with clipping of aneurysm neck, excision of the aneurysm, coiling, or wrapping

if no other method is feasible.

30.16. Mycotic aneurysms

The name *"mycotic"* originated with Osler in whose time the term referred to any infectious process[358] rather than the current usage which infers a fungal etiology. Currently accepted terminology favors **infectious aneurysm** (or bacterial aneurysm). Infectious aneurysms can, however, also occur with fungal infections[359]. Tend to form in distal (often unnamed) vessels.

Epidemiology & pathophysiology

- comprise ≈ 4% of intracranial aneurysms
- occurs in 3-15% of patients with subacute bacterial endocarditis **(SBE)**
- most common location: distal MCA branches (75-80%)
- at least 20% have or develop multiple aneurysms
- increased frequency in immunocompromised patients (e.g. AIDS) and drug users
- most probably start in the adventitia (outer layer) and spread inward

Evaluation

Blood cultures and LP may identify the infectious organism. *Table 30-15* shows typical pathogens recovered. Patients with suspected infectious aneurysm(s) should undergo echocardiography to look for signs of endocarditis.

Table 30-15 Pathogens implicated in mycotic aneurysms[360] (p 933-40)

Organism	%	Comment
streptococcus	44%	*S. viridans* (classic cause of SBE)
staphylococcus	18%	*S. aureus* (cause of acute bacterial endocarditis)
miscellaneous	6%	(pseudomonas, enterococcus, corynebacter…)
multiple	5%	
no growth	12%	
no info	14%	
total	99%	

TREATMENT

These aneurysms usually have fusiform morphology and are usually very friable, therefore surgical treatment is difficult and/or risky. Most cases are treated acutely with antibiotics which are continued 4-6 weeks. Serial angiography (at 7-10 days and 1.5, 3, 6 and 12 months, even if aneurysms seem to be getting smaller, they may subsequently increase[361] and new ones may form) helps document effectiveness of medical therapy (serial MRA may be a viable alternative in some cases). Aneurysms may continue to shrink following completion of antibiotic therapy[362]. Delayed clipping may be more feasible; indications include:

- patients with SAH
- increasing size of aneurysm while on antibiotics[363] (controversial, some say not mandatory[362])
- failure of aneurysm to reduce in size after 4-6 weeks of antibiotics[363]

Patients with SBE requiring valve replacement should have bioprosthetic (i.e. tissue) valves instead of mechanical valves to eliminate the need for risky anticoagulation.

30.17. Giant aneurysms

Definition: > 2.5 cm (≈ 1 inch) diameter. Two types: saccular (probably an enlarged "berry" aneurysm) and fusiform. Comprise 3-5% of intracranial aneurysms; peak age of presentation 30-60 years; female:male ratio = 3:1.

Drake's series of 174 giant aneurysms[364]: 35% presented as hemorrhage, with 10% showing some evidence of remote bleeding. The bleeding rate is unknown, but is probably less than the ≈ 2%/year for non-giant aneurysms.

May also present as TIAs (by reducing flow or by emboli) or as a mass. About one third have a neck amenable to clipping.

EVALUATION

Drake contends that even after thorough radiographic evaluation, actual operative visualization is the only way to definitively assess the aneurysm and its branches.

Angiogram: Often underestimates the size of the lesion secondary to thrombosed regions of the aneurysm that do not fill with contrast. CT or MRI is

required to visualize the thrombosed portion.

CT scan: Frequently have a significant amount of edema surrounding the aneurysm. May see contrast enhancement of the brain surrounding the aneurysm; probably due to increased vascularity secondary to inflammatory reaction to the aneurysm.

MRI scan: Turbulence within → complicated signal on T1WI. **Pulsation artifact** (linear distortion radiation through aneurysm) on MRI helps differentiate giant aneurysms from solid or cystic lesions.

Treatment

Options include:

1. direct surgical clipping: usually possible in only ≈ 50% of cases
2. vascular bypass of aneurysm with subsequent clipping
3. trapping
4. proximal arterial ligation (hunterian ligation)
   A. for vertebral-basilar aneurysms[241]: results in improvement of cranial nerve deficit in ≈ 95% of patients
5. wrapping: *see page 1058*

30.18. SAH of unknown etiology

Recent estimates of incidence: **7-10%**. This is a heterogeneous category, and a better term might be “angiogram-negative SAH” (*see page 1038* for requirements to be met before considering an arteriogram to be negative). The quantity of blood on CT may predict the chances of an arteriogram disclosing a cerebral aneurysm[365-368].

Patients with angiogram-negative SAH tend to be younger, less hypertensive, and more commonly male than those with positive angiography[366].

Possible causes of SAH with a negative angiogram include:

1. aneurysm that fails to be demonstrated in initial angiogram
   A. inadequate angiography, causes include:
      1. incomplete angio: *see page 1038*
         a. must see both PICA origins (1-2% of aneurysms occur here)
         b. need to cross-fill through the ACoA (*see page 1038*)

2. degradation of images due to
   a. poor patient cooperation (e.g. from agitation). Either sedate patient (use caution in non-intubated patients) or repeat the study at a later time when patient more cooperative
   b. poor quality equipment providing substandard images

B. obliteration of aneurysm by the hemorrhage

C. thrombosis of the aneurysm after SAH: *see page 1058*

D. aneurysm too small to be visualized[369]: although "microaneurysms" may be a source of SAH, their natural history and optimal treatment are unknown

E. lack of filling of aneurysm due to vasospasm (of parent artery or of aneurysmal orifice)

2. nonaneurysmal SAH from source that fails to show up on angiography. *See page 1034* for etiologies of SAH other than aneurysm (many of which may not be demonstrated on angiography), including:
   A. angiographically occult (or cryptic) vascular malformation: *see page 1105*
   B. pretruncal nonaneurysmal SAH: *see below*

Risk of rebleeding

Overall rebleed rate is 0.5%/yr, which is lower than with aneurysmal SAH or rebleeding from AVMs. There is also a smaller risk of delayed cerebral ischemia (vasospasm). Neurological outcome is likewise better.

MANAGEMENT

General measures

These patients are still at risk for the same complications of SAH as with aneurysmal SAH: vasospasm, hydrocephalus, hyponatremia, rebleeding, etc. (*see page 1040*) and should be managed as any SAH (*see page 1040*). Some subgroups may be at lower risk for complications and may be managed accordingly (e.g. see *Pretruncal nonaneurysmal SAH (PNSAH)* below).

Repeat angiography

Yield of positive second angiogram after technically adequate negative study: 1.8-9.8%)[370] in early (pre-CT) studies, 2-24% quoted more recently[369],

[371], [372]. CT scan findings are helpful in the decision to repeat angiography[373]. 70% of cases with diffuse SAH and thick layering of blood in the anterior interhemispheric fissure were associated with an ACoA aneurysm that showed up on repeat angiography[367]. The absence of blood on CT (performed within 4 days of SAH), or thick blood in the perimesencephalic cisterns alone (*see below*) were unlikely to be associated with a missed aneurysm.

Recommendations regarding repeat angio:

1. repeat angio after ≈ 10-14 days (allows vasospasm & some clot to resolve)[A]
   A. technically adequate 4 vessel angiogram is negative, and evidence for SAH is strong
   B. original angio was incomplete or if there are suspicious findings
2. if CT localizes blood clot to particular area, place special attention to this area on repeat angio
3. do not repeat angio for classic pretruncal SAH (*see below*) or if no blood on CT
4. patients are usually kept in the hospital 10-14 days while waiting for repeat angio (to watch for and manage complication of SAH or rebleeding)

A. between 5-10 days there is decreased chance of seeing an aneurysm because of vasospasm; angiography at ≈ day 10 permits surgery to be done if needed ≈ at day 14 which is about the earliest time after the "no-op" window of day 3-12

Third arteriogram:

If the 1st 2 arteriograms are negative, and the history is suggestive of aneurysmal SAH, a 3rd arteriogram 3-6 months after SAH has ≈ 1% chance of showing a source of bleeding.

Other studies

1. imaging studies of the brain: MRI (with MRA if available) or CT (with angio-CT if available). This may visualize an aneurysm that fails to show up on angiography, and may identify other sources of SAH such as angiographically occult vascular malformation (*see page 1105*), tumor…
2. tests to rule-out spinal AVM: a rare cause of intracerebral SAH (*see page*

507)

A. spinal MRI: cervical, thoracic and lumbar
B. spinal angiography: too difficult and risky to be justified in most cases of angio negative SAH. Consider in cases with high suspicion of spinal source

Surgical exploration

Advocated by some for cases of SAH with CT findings compatible with an aneurysmal source in which a suspicious area is demonstrated angiographically[369] with careful explanation to the patient and family of the possibility of negative operative findings.

30.19. Nonaneurysmal SAH

For etiologies of SAH other than aneurysm, *see page 1034*.

PRETRUNCAL NONANEURYSMAL SAH (PNSAH)

Née perimesencephalic nonaneurysmal SAH[374]. The suggestion to change the name to pretruncal nonaneurysmal SAH was proposed because improved neuroimaging techniques have shown the true anatomic localization of the blood to be in front of the brain stem (truncus cerebri) centered in front of the pons rather than perimesencephalic[375]. Blood often extends into the interpeduncular or premedullary cisterns.

A distinct entity considered to be a benign condition with good outcome and less risk of rebleeding and vasospasm than other patients with SAH of unknown etiology[376] (no **rebleeding** occurred in 37 patients with PNSAH and 45 months mean follow-up[377], nor in 169 patients with 8-51 months follow-up[372]; **vasospasm** has been reported in only 3 patients and may have been related to cerebral angiography rather than the PNSAH, and although it is low, the incidence of angiographic vasospasm may be higher than originally thought[378]).

The actual etiology has yet to be determined, but it may be secondary to rupture of a small perimesencephalic vein or capillary[378].

Presentation

Patients may present with severe paroxysmal H/A, meningismus,

photophobia, and nausea. Loss of consciousness is rare. These patients are usually not critically ill (all were grade 1 or 2), however, complications such as hyponatremia or cardiac abnormalities may occur. Preretinal hemorrhages and sentinel H/A have not occurred. CT and/or MRI demonstrate characteristic findings (*see below*) although it may initially be missed on CT[378], and LP may yield bloody CSF. All have negative angiography.

Epidemiology

PNSAH has been reported to comprise 20-68% of cases of angiogram-negative SAH[376, 379] (depending on the timing of CT, adequacy of angiography, and the definition of PNSAH). However, the true incidence is probably more in the range of 50-75%[372].

The reported age range is 3-70 years (mean: 50 yrs)[372, 52-59]% are male, and pre-existing HTN was present in 3-20% of patients.

Relevant anatomy

Posterior fossa cisterns:

The perimesencephalic cisterns include: interpeduncular, crural, ambient and quadrigeminal cisterns. The prepontine cistern lies immediately anterior to the pons.

Liliequist's membrane **(LM)**[380]:

Basically considered to separate the interpeduncular cistern from the chiasmatic cistern[381] (forming a competent barrier in only 10-30%). In further detail, the superior leaflet of LM (diencephalic membrane) separates the interpeduncular cistern from the chiasmatic cistern medially and from the carotid cisterns laterally[382, 383]. The inferior leaflet (the mesencephalic membrane) separates the interpeduncular from the prepontine cistern.

The diencephalic membrane is thicker and is more often competent, effectively isolating the chiasmatic cistern. However, the carotid cisterns often communicate with the crural cisterns and in turn with the interpeduncular cistern[383].

Thus, blood in the carotid or prepontine cistern is compatible with a low-pressure pretruncal source of bleeding, however, blood in the <u>chiasmatic cistern</u> should raise concern about aneurysmal rupture.

Table 30-16 CT or MRI criteria for PNSAH[378, 384]

1.	epicenter of hemorrhage immediately anterior to brain stem (interpeduncular or prepontine cistern)
2.	there may be extension into anterior part of ambient cistern or basal part of the sylvian fissure
3.	absence of complete filling of anterior interhemispheric fissure
4.	no more than minute amounts of blood in lateral portion of sylvian fissure
5.	absence of frank intraventricular hemorrhage (small amounts of blood sedimenting in the occipital horns of the lateral ventricles is permissible)

Diagnostic criteria

Without knowledge of the actual substrate of PNSAH, the following suggested diagnostic criteria must be viewed as empiric (adapted[372]):

1. CT or MRI scan performed ≤ 2 days from ictus meeting the criteria shown in *Table 30-16* (later scans render the diagnosis unreliable, e.g. washout could cause an aneurysmal SAH to fit the criteria). This criteria implies that blood should be contained inferior to Liliequist's membrane **(LM)** (i.e. perimesencephalic and/or prepontine cisterns). Extension into the suprasellar cistern is common. Significant amounts of blood penetrating LM to the chiasmatic, sylvian, or interhemispheric cisterns should be viewed with suspicion
2. a negative high-quality 4-vessel cerebral angiogram[385] (radiographic vasospasm is common, and does not preclude the diagnosis nor does it mandate repeat angiography). NB: ≈ 3% of patients with a ruptured basilar bifurcation aneurysm meet the criteria of *Table 30-16*[386], therefore an initial arteriogram is mandatory
3. appropriate clinical picture: no loss of consciousness, no sentinel H/A, SAH grade 1 or 2 (see *Grading SAH*, page 1039). Variance from this should raise suspicion of alternate pathogenesis

Repeat angiography

Controversial. Angiography carries ≈ 0.2-0.5% risk of permanent neurologic deficit in this population[372]. Most experts agree that repeat angiography is not indicated in patients meeting the criteria of PNSAH[371, 385] (although others recommend repeat angiography in all surgical candidates[369, 387]). One should probably repeat the study if any uncertainty exists or if there is a history of a condition associated with increased risk of cerebral aneurysms[378].

Treatment

Optimal treatment is not known with certainty. The low risk of rebleeding

and delayed ischemia suggests that extreme measures are not indicated. The following recommendations are made[372, 378] (period not specified):

1. symptomatic treatment
2. cardiac monitoring
3. electrolyte monitoring for hyponatremia
4. follow patient clinically (and if appropriate, with repeat imaging studies) to rule-out hydrocephalus (transient ventricular enlargement is common, however, hydrocephalus requiring shunting is rare (only ≈ 1%)[372])
5. ✖ not recommended
   A. hyperdynamic therapy
   B. calcium channel blockers: use has not been investigated in PNSAH, but is probably not warranted due to low incidence of vasospasm
   C. activity restrictions (except in cases of increasing H/A with mobilization)
   D. anticonvulsants
   E. reduction of blood pressure below normal
   F. surgical exploration

30.20. Pregnancy & intracranial hemorrhage

Intracranial hemorrhage (subarachnoid or intraparenchymal) is a rare occurrence during pregnancy (estimated range of incidence: 0.01-0.05% of all pregnancies[388]) and yet is responsible for 5-12% of maternal deaths during pregnancy.

Intracranial hemorrhage of pregnancy **(ICHOP)** commonly occurs in the setting of eclampsia, and is more commonly intraparenchymal[389] and may be associated with loss of cerebrovascular autoregulation (*see page 73*). Symptoms of eclampsia with or without ICHOP include H/A, mental status changes, and seizures.

A literature review of 154 reported cases of ICHOP-related SAH revealed 77% were aneurysmal and 23% were from ruptured AVM (other series show the percentage of AVMs range from 21-48%). Mortality is ≈ 35% for aneurysmal and ≈ 28% for AVM hemorrhage (the latter being higher than in non-gravid patients). There is an increasing tendency for bleeding with advancing gestational age for both aneurysms and AVMs (earlier it had been asserted that

this held true for aneurysms only[390]).

Patients with ICHOP having AVMs tend to be younger than those with aneurysm, paralleling the occurrence in the general population. One major oft-quoted study showed an increased risk of hemorrhage from AVMs during pregnancy[391] (citing an 87% hemorrhage rate), however another investigation disputes this assertion[392], and found the risk of hemorrhage to be 3.5% during the pregnancy in patients with no history of hemorrhage, or 5.8% in those with previous hemorrhage (however, this study may suffer from significant selection bias[393]). Literature review[388] found a risk of recurrent hemorrhage following ICHOP from aneurysm or AVM during the remainder of the pregnancy was 33-50%.

Management modifications for pregnant patients

1. neuroradiologic studies
   A. CAT scan: with shielding of the fetus, CAT scanning of the brain produces minimal radiation exposure
   B. MRI: generally felt to have low potential for complications, however, many centers will not do MRI during first trimester. The safety of gadopentetate dimeglumine (Magnevist®) has not been studied in human pregnancy (classified by FDA as a Class III drug - not recommended for use during pregnancy, but may be used if benefits outweigh potential risks)
   C. angiography: with shielding of the fetus, radiation exposure is minimal. Iodinated contrast agents pose little risk to the fetus, The mother should be well hydrated during and after the study[388]
2. antiepileptic drugs: see *Pregnancy and antiepileptic drugs*, page 419
3. diuretics: the use of mannitol in pregnancy should be avoided to prevent fetal dehydration and maternal hypovolemia with uterine hypoperfusion
4. antihypertensives: nitroprusside should not be used in pregnancy
5. nimodipine is potentially teratogenic in animals, the effect on humans is unknown. It should be used only when the potential benefit justifies the risk

Neurosurgical management[388]

The currently recommended treatment of a ruptured aneurysm in the pregnant patient is surgical clipping. Treatment of hemorrhage from AVM is

more controversial. A number of authors recommend basing the decision of treatment on neurosurgical rather than obstetrical considerations.

Obstetric management following ICHOP

Earlier recommendations were to perform C-section to avoid the hemodynamic stresses of labor and vaginal delivery, however, the risk of hemorrhage is not significantly different between vaginal delivery and C-section. Several reports have indicated that the fetal and maternal outcome is no different for vaginal delivery vs. C-section, and is probably more dependent on whether the offending lesion has been treated. C-section may be used for fetal salvage for a moribund mother in the third trimester. During vaginal delivery, the risk of rebleeding may be reduced by the use of caudal or epidural anesthesia, shortening the 2nd stage of labor, and low forceps delivery if necessary.

30.21. References

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NOTES

31. Vascular malformations

This designation encompasses a number of non-neoplastic vascular lesions of the CNS. The four types described by McCormick in 1966 are[1]:

1. arteriovenous malformations **(AVMs)**[A]: *see below*
2. venous angioma (*see page 1104*) } also see *Angiographically occult vascular malformations*, page 1105
3. cavernous malformation (*see page 1106*) } also see *Angiographically occult vascular malformations*, page 1105
4. capillary telangiectasia (*see page 1106*) } also see *Angiographically occult vascular malformations*, page 1105

A. sometimes referred to as *pial* AVMs to distinguish e.g. from *dural* AVMs

A possible fifth category is **direct fistula** AKA arteriovenous fistula (AV-fistula, not AVM). Single or multiple dilated arterioles that connect directly to a vein without a nidus. These are high-flow, high-pressure. Low incidence of hemorrhage. Usually amenable to interventional neuroradiological procedures. Examples include:

1. vein of Galen malformation (aneurysm): *see page 1112*
2. dural AVM: *see page 1109*
3. carotid-cavernous fistula: *see page 1113*

31.1. Arteriovenous malformation

Key concepts:

> • dilated arteries and veins with dysplastic vessels. Arterial blood flows directly between them with no capillary bed & no intervening neural parenchyma in nidus
> • in adulthood, AVMs are medium-to-high pressure and high-flow

- usually presents with hemorrhage, less often with seizures
- not congenital. Risk of bleeding: ≈ 2-4% per year
- demonstrable on angiography, MRI, or CT (especially with contrast)
- main treatment options: stereotactic radiosurgery (usually for deep lesions < 3 cm dia) or surgical excision

Description

An abnormal collection of blood vessels wherein arterial blood flows directly into draining veins without the normal interposed capillary beds. There is no brain parenchyma contained within the nidus. AVMs are not congenital, they tend to enlarge somewhat with age and often progress from low flow juvenile lesions to medium-to-high-flow high-pressure lesions in adulthood. AVMs appear grossly as a "tangle" of vessels, often with a fairly well circumscribed center (nidus), and draining "red veins" (veins containing oxygenated blood). May be classified as:

1. parenchymal AVMs (discussed below). Subclassified as:
   A. pial
   B. subcortical
   C. paraventricular
   D. combined
2. pure dural AVM (*see page 1109*)
3. mixed parenchymal and dural (rare)

Epidemiology

Prevalence: probably slightly greater than the usually quoted 0.14%.

Slight male preponderance.

15-20% of patients with Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia) have cerebral AVMs.

Comparison to aneurysms[2]

AVM:aneurysm ratio in U.S. is 1:5.3 (pre-CT era data). The average age of patients diagnosed with AVMs is ≈ 33 yrs, which is ≈ 10 yrs younger than aneurysms[3]. 64% of AVMs are diagnosed before age 40 (c.f. 26% for aneurysms).

Presentation

1. hemorrhage (most common)[4]: 50% (61% quoted elsewhere[2], compared to 92% for aneurysms) (*see below*)
2. seizures
3. mass effect: e.g. trigeminal neuralgia due to CPA AVM
4. ischemia: by steal
5. H/A: rare. AVMs may occasionally be associated with migraines. Occipital AVMs may present with visual disturbance (typically hemianopsia or quadrantanopsia) and H/A that are indistinguishable from migraine[5]
6. bruit: especially with dural AVMs (*see page 1109*)
7. increased ICP
8. findings limited almost exclusively to peds, usually with large midline AVMs that drain into an enlarged vein of Galen ("vein of Galen malformation", *see page 1112*):
   A. hydrocephalus with macrocephaly: due to compression of Sylvian aqueduct by enlarged vein of Galen or to increased venous pressure
   B. congestive heart failure with cardiomegaly
   C. prominence of forehead veins (due to increased venous pressure)

Hemorrhage

Peak age for hemorrhage is between 15-20 yrs[2]. **10% mortality**, **30-50% morbidity**[6] (neurological deficit) from each bleed. For a discussion of hemorrhage during pregnancy, see *Pregnancy & intracranial hemorrhage*, page 1086.

Hemorrhage location with AVMs

1. intraparenchymal (CH): 82% (the most common site of bleeding)[7]
2. intraventricular hemorrhage:
   A. usually accompanied by ICH as the result of rupture into the ventricle
   B. pure IVH (with no ICH) may indicate an intraventricular AVM
3. subarachnoid: SAH may also be due to rupture of an aneurysm on a feeding artery (common with AVMs) *see page 1034*
4. subdural: uncommon. May be the sourced of a spontaneous SDH (*see page 902*)

Hemorrhage rate based on nidus depth, venous drainage & prior bleed

Breakdown of the risk of bleeding based on history of prior bleeding, venous drainage pattern, and nidus location using data from Stapf et al. is shown in *Table 31-1*.

Hemorrhage rate related to AVM size

Small AVMs tend to present more often as hemorrhage than do large ones[8, 9]. It was postulated that larger AVMs presented as seizure more often simply because their size made them more likely to involve the cortex. How-ever, small AVMs are now thought to have much higher pressure in the feeding arteries[9]. Conclusion: small AVMs are more lethal than larger ones.

Table 31-1 Annual average hemorrhage rates for various AVM subgroups[101]

Venous drainage	No prior hemorrhage	Prior hemorrhage	Nidus location
No deep venous drainage	0.9%	4.5%	Not deep
	3.1%	14.8%	Deep
Deep venous drainage	8.0%	34.4%	
	2.4%	11.4%	Not deep

Hemorrhage rate related to Spetzler-Martin grade

Controversial. Some studies show increased risk with Spetzler-Martin (S-M) grade (*see page 1101*) 4-5 AVMs[10] (high grade), others show the opposite effect as:

S-M grade 1-3: annual risk of hemorrhage is 3.5%.

S-M grade 4-5: annual risk of hemorrhage is 2.5%.

Annual and lifetime risk of hemorrhage and recurrent hemorrhage

The average risk of hemorrhage from an AVM is ≈ 2-4% per year[11]

(reminder: risk varies by AVM size, *see above*). The risk of bleeding over the remainder of one's life is given by *Eq 31-1*[A].

$$\text{risk of bleeding (at least once)} = 1 - (\text{annual risk of not bleeding})^{\text{expected years of remaining life}} \quad \textbf{Eq 31-1}$$

A. this analysis includes a number of assumptions including: a constant risk of rebleeding even early after an initial bleed, no change in risk during the lifetime (which may not be true in pregnancy), no difference in risk for various AVM locations or age groups

Where the *annual* risk of *not* bleeding is equal to 1 – the annual risk of bleeding. For example, if a 3% annual risk of bleeding is used as an average, and the remaining life expectancy is 25 years, the result is as illustrated in *Eq 31-2*.

$$\text{risk of bleeding at least once (in 25 years)}^{*} = 1 - 0.97^{25} = 0.53 = 53\% \quad \textbf{Eq 31-2}$$

A simple to apply first approximation to *Eq 31-1* is shown in *Eq 31-3*.

$$\text{risk of bleeding (at least once)}^{*} \approx 105 - \text{age in years} \quad \textbf{Eq 31-3}$$

* *Eq 31-2* & *Eq 31-3* assume a 3% per year bleeding rate

Table 31-2 shows the risk for various ages using *Eq 31-1* (longevity is taken from insurance life-tables).

A study of 166 symptomatic AVMS with long average followup (mean: 23.7 yrs)[3] found the risk of major bleeding was constant at **4% per year**, independent of whether the AVM presented with or without hemorrhage. The mean time between presentation and hemorrhage was 7.7 yrs. The mortality rate was 1% per year, and the combined major morbidity and mortality rate was 2.7% per year.

Older studies may suffer from smaller numbers[8] or short follow-up (mean: 6.5 yrs)[2, 4]. These studies suggested a higher risk of (re)bleeding depending on whether the initial presentation was hemorrhage (≈ 3.7% per year) vs. seizure (1-2% per year).

The hemorrhage risk may be higher in peds or with p-fossa AVMs[11].

Table 31-2 Lifetime risk of hemorrhage*

Age at presentation	Estimated years to live†	Lifetime risk of hemorrhage		
		For 1% annual risk‡	For 2% annual risk	For 3% annual risk
0	76	53%	78%	90%
15	62	46%	71%	85%
25	52	41%	65%	79%
35	43	35%	58%	73%
45	34	29%	50%	64%
55	25	22%	40%	53%
65	18	16%	30%	42%
75	11	10%	20%	28%
85	6	5.8%	11%	17%

* modified from reference[11]

† based on 1992 Preliminary Life tables prepared by Metropolitan Life Insurance Company

‡ 1% annual risk is also presented because it may be appropriate for incidental aneurysms (*see page 1077*)

Rebleeding: Reported rebleeding rate in the first year after hemorrhage was 6% in one series[12], 18% in another series[13] which declined to 2% per year after 10 years, and in another large series[3] the annual rate was 4% and did not vary regardless of presentation.

Seizures

The younger the patient at the time of diagnosis, the higher the risk of developing convulsions. 20 yr risk: diagnosis at age 10-19 → 44% risk; age 20-29 → 31%; age 30-60 → 6%. Patients presenting with hemorrhage have 22% risk of developing epilepsy in 20 yrs. No AVM found incidentally or presenting with neuro deficit developed seizures[8].

AVMs and Aneurysms

7% of patients with AVMs have aneurysms. 75% of these are located on major feeding artery (probably from increased flow)[8]. These aneurysms may be classified into 1 of 5 types shown in *Table 31-3*. Aneurysms also may form within the nidus or on draining veins. When treating tandem AVMs and aneurysms, the symptomatic one is usually treated first (when feasible, both may be treated at the same operation)[14]. If it is not clear which bled, the odds are that it was the aneurysm. Although a significant number (≈ 66%) of related aneurysms will regress following removal of the AVM, this does not always occur. In one series, none of the 9 associated aneurysms ruptured or enlarged following AVM removal[14]

Table 31-3 Categories of aneurysms associated with AVMs*[14]

Type	Aneurysm location
I	proximal on ipsilateral major artery feeding AVM
IA	proximal on major artery related but contralateral to AVM
II	distal on superficial feeding artery
III	proximal or distal on deep feeding artery (“bizarre”)
IV	on artery unrelated to AVM

* excludes intranidal and venous aneurysms

EVALUATION

CT

Unenhanced brain CT is the best study to rule-out acute hemorrhage. Can also demonstrate calcifications within the lesion. Adding a contrast CT will show enhancement within the vessels, and can delineate the nidus (dense central area of an AVM).

MRI

1. flow void on T1WI or T2WI within the AVM
2. feeding arteries
3. draining veins
4. increased intensity on partial flip-angle (to differentiate signal dropout on T1WI or T2WI from calcium)
5. significant edema around the lesion may indicate a tumor that has bled rather than an AVM
6. gradient echo sequences (GRASS…) help demonstrate surrounding hemosiderin which suggests a previous significant hemorrhage
7. a complete ring of low density (due to hemosiderin) surrounding the lesion suggests AVM over neoplasm

ANGIOGRAPHY

1. tangle of vessels
2. large feeding artery
3. large draining veins

4. draining veins are visualized in the same images as arteries (arterial phase)

Most, but not all AVMs show up on angiography (see *Angiographically occult vascular malformations*, page 1105). Fewer cavernous malformations and venous angiomas do.

Table 31-4 Spetzler-Martin AVM grading system[15]

Graded feature	Points
Size*	
small (< 3 cm)	1
medium (3-6 cm)	2
large (> 6 cm)	3
Eloquence of adjacent brain	
non-eloquent†	0
eloquent†	1
Pattern of venous drainage‡	
superficial only	0
deep	1

* largest diameter of nidus on non-magnified angiogram (is related to and therefore implicitly includes other factors relating to difficulty of AVM excision, e.g. number of feeding arteries, degree of steal, etc.)

† eloquent brain: sensorimotor, language and visual cortex; hypothalamus and thalamus; internal capsule; brain stem; cerebellar peduncles; deep cerebellar nuclei

‡ considered superficial if all drainage is through cortical venous system; considered deep if any or all is through deep veins (e.g. internal cerebral vein, basal vein, or pre-central cerebellar vein)

Grading

Spetzler-Martin grade of AVMs

Grade = sum of points from *Table 31-4*, ranges from 1 to 5. A separate grade 6 is reserved for untreatable lesions (by any means: surgery, SRS…), resection of these would almost unavoidably be associated with disabling deficit or death. May not be applicable to pediatrics (AVMs are immature and change with time; AVMs mature at ≈ age 18 yrs and tend to become more compact).

Outcome based on Spetzler-Martin grade: 100 consecutive cases operated by an expert (Spetzler) had the outcomes shown in *Table 31-5* (no deaths).

★ Spetzler has since advocated not treating grade 5 AVMs (by any means)[]. Surgery is not the optimal treatment for many S-M grade 4 AVMs. Recommendation for grade 4 & 5 AVMs: angiogram every 5 years to look for

the development of feeding vessel aneurysm or outflow stenosis, both of which are risk factors for problems.

TREATMENT

Options and some pros and cons of each include:

1. surgery: the treatment of choice for AVMs. When surgical risk is unacceptably high, alternative procedures may be an option
   A. pros: eliminates risk of bleeding almost immediately. Seizure control improves
   B. cons: invasive, risk of surgery, cost (high initial cost of treatment may be offset by effectiveness or may be increased by complications)
2. radiation treatment
   A. conventional radiation: effective in ≈ 20% or less of cases[16, 17]. Therefore not considered effective therapy
   B. stereotactic radiosurgery **(SRS)**: accepted for some small (≤ 2.5-3 cm nidus), deep AVMs (see *Stereotactic radiosurgery & radiotherapy*, page 773)
      1. pros: done as an outpatient, non-invasive, gradual reduction of AVM flow, no recovery period
      2. cons: takes 1-3 years to work (during that time there is a risk of bleeding, controversial whether it is increased or decreased), limited to lesions with nidus ≤ 3 cm
3. endovascular techniques: e.g. embolization (*see below*)
   A. pros: facilitates surgery
   B. cons: sometimes inadequate by itself to permanently obliterate AVMs, induces acute hemodynamic changes, may require multiple procedures, embolization prior to SRS reduces the obliteration rate from 70% (without embolization) to 47% (with embolization)[18]
4. combination techniques: e.g. embolization to shrink nidus then stereotactic radiosurgery

Table 31-5 Surgical outcome by Spetzler-Martin grade operated on by Spetzler

Grade	No.	No deficit	Minor deficit*	Major deficit†
1	23	23 (100%)	0	0
2	21	20 (95%)	1 (5%)	0
3	25	21 (84%)	3 (12%)	1 (4%)
4	15	11 (73%)	3 (20%)	1 (7%)
5	16	11 (69%)	3 (19%)	2 (12%)

* minor deficit: mild brainstem deficit, mild aphasia, mild ataxia

† major deficit: hemiparesis, increased aphasia, homonymous hemianopsia

Considerations to take into account in managing AVMs:

1. associated aneurysms: on feeding vessels, draining veins or intranidal
2. flow: high or low
3. age of patient
4. history of previous hemorrhage
5. size and compactness of nidus
6. availability of interventional neuroradiologist
7. general medical condition of the patient

EMBOLIZATION

Used as an initial procedure, embolization facilitates surgery[19] and possibly SRS. It is usually inadequate by itself to treat conventional AVMs (may recanalize later), however, is useful as the primary treatment of direct fistulas (*see page 1098*). May also be appropriate treatment for vein of Galen aneurysms and pial fistulas.

Agents

1. **Onyx**[20, 21]: ethylene-vinyl alcohol (EVOH) copolymer (ethylene and vinyl alcohol) dissolved in dimethyl sulfoxide (DMSO) with micronized tantalum (for radioopacity). Not an adhesive. Has generally supplanted other materials for AVMs. Supplied in pre-mixed ready-to-use vials in which the number (e.g. Onyx-18) corresponds to the nominal viscosity (as measured in centistokes) which the manufacturer controls by altering the EVOH concentration. Preparations typically used: Onyx-18, Onyx-34 (both for AVMs) and Onyx-500 (for aneurysms). Prior to use, the product must be shaken on a mixer for at least 20 minutes. Liquid Onyx is delivered through a DMSO primed microcatheter. Onyx solidifies through

the process of precipitation which is initiated when it comes into contact with an aqueous solution (e.g. blood, body fluids, normal saline, water) as the DMSO solvent rapidly diffuses out. Pathologic changes (similar to the acrylates) include: endothelial necrosis, acute inflammatory reaction, foreign body giant cells. Onyx is bright on T1WI MRI

2. particulates: polyvinyl alcohol (PVA) particles. Nidus obliteration is slower than with liquid agents. During this time before complete obliteration, the nidus is exposed to increased pressures, which theoretically temporarily increases the risk of hemorrhage[20]
3. acrylates: adhesives. Risk of inadvertently gluing catheter to artery
   A. N-butyl cyanoacrylate (NBCA): often mixed with Ethiodol in various pro-portions to delay polymerization time
   B. isobutyl-2-cyanoacrylate (no longer available)

Timing and technical considerations before definitive treatment

When used before surgery, wait 3-30 days before operating (if symptoms develop, wait for patient to recover).

When used before SRS, wait ≈ 30 days (the immediate post-embolization angio usually looks better, and might result in parts of the AVM being left out of the desired iso-center). Avoid using radioopaque material in the embolization mixture because this can render CT almost unusable for SRS treatment planning.

Delayed post embolization deterioration

Etiologies include:

1. hemorrhage
2. steal
3. retrograde venous thrombosis

Risks

Berenstein's analysis of his series (1985-90) yielded the risks shown in *Table 31-6*.

Long term obliteration

When complete obliteration of the AVM by embolization used alone persists

on arteriography at 6 months, it will remain so on the 2 year arteriogram. If there is AVM still visible at 6 months, it will not progress on its own to obliteration at 2 years.

Table 31-6 Risks of AVM embolization

risk	%
death*	1-2%
severe deficit	1.5%
mild deficit	9%
transient deficit	11%
1st time hemorrhage after embolization	3%
rehemorrhage after embolization	7%
new seizure	3%

* 0.5% in older series

Surgical treatment

Pre-Op Medical management: Before direct surgical treatment, patient should ideally be pre-treated with propranolol 20 mg PO QID for 3 days to minimize post-op normal perfusion pressure breakthrough (postulated cause of post-operative bleeding and edema[22], *see below*). Labetalol has also been used perioperatively to keep MAP 70-80 mm Hg[23].

Booking the case - craniotomy for AVM:

BOOKING

Also see defaults & disclaimers (*page v*).

1. position: (depends on location of AVM), radiolucent headholder
2. pre-op embolization (by neuroendovascular interventionalist): typically 24-48 hours pre-op
3. intraoperative angiography (optional)
4. equipment
   A. microscope (with ICG capability if used)
   B. image-guided navigation: primarily for the bone flap placement
5. blood availability: type and cross 2 U PRBC
6. post op: ICU
7. consent (in lay terms for the patient - not all-inclusive):

A. procedure: surgery to open the skull and remove the abnormal tangle of blood vessels in the brain, intraoperative angiography

B. alternatives: stereotactic radiosurgery, endovascular techniques (not considered definitive treatment for most AVMs, but often used as an adjunct)

C. complications: (usual craniotomy complications - *see page v*) *plus* stroke (the main concern), bleeding intra-op (requiring transfusion) and post-op, neurologic deficit related to the area of AVM location, failure to be able to remove entire AVM, recurrence in future

Basic tenets of AVM surgery

1. wide exposure
2. occlude feeding (terminal) arteries before draining veins (lesions with a single draining vein can become impossible to deal with if premature blockage of the draining vein occurs, e.g. by kinking, coagulation)
3. excision of whole nidus is necessary to protect against rebleeding (occluding feeding arteries is not adequate)
4. identify and spare vessels of passage and adjacent (uninvolved) arteries
5. dissect directly on nidus of AVM, work in sulci and fissures whenever possible
6. in lesions that are high-flow on angiography, consider preoperative embolization
7. lesions with supplies from multiple vascular territories may require staging
8. clip accessible aneurysms on feeding arteries

Delayed postoperative deterioration

May be due to any of the following:

1. **normal perfusion pressure breakthrough** 22: characterized by post-op swelling or hemorrhage. Thought to be due to loss of autoregulation, although this theory has been challenged[24]. Risk may be reduced by pre-op medication (*see above*)
2. **occlusive hyperemia** 25: in the immediate post-op period probably due to obstruction of venous outflow from adjacent normal brain, in a delayed presentation may be due to delayed thrombosis of draining vein or dural sinus[26]. Risk may be elevated by keeping the patient “dry” post-op

3. rebleeding from a retained nidus of AVM
4. seizures

Follow-up of treated AVMs

When satisfactory complete angiographic obliteration of an AVM has been accomplished, recommended follow-up is with catheter angiogram (not CTA or MRA) at 1 & 5 years post treatment.

31.2. Venous angiomas

Key concepts:

- a vascular malformation that is part of the venous drainage of the involved area with intervening brain present. Therefore direct treatment is rarely indicated
- low-flow, low-pressure
- usually demonstrable on angiography as a starburst pattern
- rarely symptomatic: seizures rare, hemorrhage even more uncommon. Venous infarcts may occur (controversial)
- may have an associated cavernous malformation which is more likely to be symptomatic (*see page 1106*)

AKA venous malformation or (developmental) venous anomaly. A tuft of medullary veins that converge into an enlarged central trunk that drains either to the deep or superficial venous system. The veins lack large amounts of smooth muscle and elastic. No abnormal arteries are found. There is neural parenchyma between the vessels. Most common in regions supplied by the MCA[27] or in the region of the vein of Galen. They may be associated with a cavernous malformation (*see page 1106*). Non hereditary. These are low-flow and low-pressure.

Most are clinically silent, but rarely seizures and even less frequently hemorrhage may occur. Venous infarcts have been described, but may be coincidental. If symptoms are present, look for an associated cavernous malformation (GRASS MRI images may reveal some cavernous malformations that might otherwise be occult).

MRI

There may be some T2 hyperintensity on FLAIR.

Angiogram

Occasionally may be angiographically occult, however, they classically produce a distinct **caput medusae** (other descriptive terms include: a hydra, spokes of a wheel, a spider, an umbrella, a mushroom, or a sunburst or starburst)[28 (p 1471)]. Other angiographic characteristics: appears as a long draining vein (longer than a normal vein) draining an excessive amount of brain tissue (it is theorized that venous restrictive disease occurs because of the length), arterial phase should show no AV shunting (characteristic of AVM).

Treatment

In general, these should not be treated as they are the venous drainage of the brain in that vicinity. If surgery is indicated for associated cavernous malformations, the angioma should be left alone. Surgery for the angioma itself is reserved only for documented bleeding or for intractable seizures definitely attributed to the lesion.

31.3. Angiographically occult vascular malformations

Terminology is controversial.

Recommendation: use the term "**angiographically occult** (or **cryptic**) **vascular malformations" (AOVM)** to refer to cerebrovascular malformations that are not demonstrable on technically satisfactory cerebral angiography (i.e. good quality cut-films, with subtraction views, and the following as appropriate: magnification, angiotomography, rapid serial angiograms or delayed films)[29]. Many lesions have large patent vessels at surgery in spite of negative angiography[30]. Other imaging modalities (i.e. CT, MRI) may be able to reveal these lesions. Although often used interchangeably, the term "occult malformation" (omitting the word "angiographically") is suggested for use with lesions that also do not appear on other imaging modalities.

The reasons for a vascular lesion being angiographically cryptic include:

1. lesion that have hemorrhaged
   A. the bleeding may obliterate the lesion: difficult to substantiate[31]

B. the clot may compress the lesion[31] which may reopen as clot dissolves

2. sluggish flow
3. small size of the abnormal vessels
4. may require very late angiographic films to visualize due to late filling

Epidemiology

Incidence of AOVM has been estimated as ≈ 10% of cerebrovascular malformations[27]. AOVMs were found at necropsy in 21 (4.5%) of 461 patients with spontaneous intracranial hemorrhage **(ICH)**[32], but refinements in angiography have occurred since this 1954 report.

The average age at diagnosis in one literature review[29] was 28 yrs.

Presentation

AOVM most often present with seizures or H/A. Less commonly they may present with progressive neurologic symptoms (usually as a result of spontaneous ICH)[33]. They may also be discovered incidentally.

The natural history of this group of lesions is not accurately known.

Table 31-7 Prevalence of subtypes of AOVM

Type	%
AVM	44-60%
cavernous angioma	19-31%
telangiectasias	4-12%
venous angioma	9-10%

Histological types of AOVM

No difference in presentation, CT appearance, or surgical prognosis was found among the following subtypes[34] (the first 4 are the classic pathologic subtypes). The prevalence of each of these lesions[34, 35] is shown in *Table 31-7*.

1. **arteriovenous malformation (AVM)**: the most common AOVM (*see page 1098*)
2. **venous angiomas**: most of these are <u>not</u> angiographically occult (*see above*)
3. **cavernous malformations**: thin walled sinusoids without interstitial cerebral parenchyma[27] (only rarely demonstrable angiographically[33]) (*see below*)

4. **capillary telangiectasia**: the least well understood AOVM. Slightly enlarged capillaries with low flow. Cannot be imaged on any radiographic study. Usually incidentally found at necropsy without clinical significance (risk of hemorrhage is very low, except possibly in brain stem). Has intervening neural tissue[27] (unlike cavernous malformations). Usually solitary, but may be multiple when seen as a part of a syndrome: Osler-Weber-Rendu (*see below*), Louis - Barr (ataxia telangiectasia), Myburn-Mason, Sturge-Weber. Should not be treated
5. mixed or unclassified angiomas: 11% of AOVM[34]

Osler-Weber-Rendu syndrome

AKA hereditary hemorrhagic telangiectasia **(HHT)**, a rare autosomal dominant genetic disorder of blood vessels affecting ≈ 1 in 5,000 people. 95% have recurrent epistaxis. Cerebrovascular malformations **(CVM)** include: telangiectasias, AVMs (the most common CVM, seen in 5-13% of HHT patients[36]), venous angiomas and aneurysms. Patients are also prone to pulmonary arteriovenous fistulas with associated risk of paradoxical cerebral embolism which predisposes to embolic stroke and cerebral abscess formation (*see page 350*).

Imaging

CT: May show a well demarcated homogeneous or mottled high density[33] (high density due to hematoma, calcification, thrombosis, hemosiderin deposition, alterations in BBB, and/or increased blood volume[29]) with some form of contrast enhancement (around or within lesion) in 17 of 24 patients[33]. Surrounding edema or mass effect is rare (except in cases that have recently hemorrhaged).

MRI: May demonstrate previous hemorrhage(s)[37], (may be important when the presence of multiple occurrences affects therapeutic choices). T2WI finding: reticulated core of increased and decreased intensity, a prominent surrounding rim of reduced intensity may be present (due to hemosiderin laden macrophages from previous hemorrhages). GRASS image demonstrates flow related enhancement in ≈ 60% of cases, which allows signal dropout from flowing blood on other sequences to be differentiated from that due to calcium (and thus, bone) or air (limitations: hemosiderin causes signal dropout, and slow inplane flow does not enhance)[38].

Treatment

Surgery is indicated mainly for evacuation of hematoma or diagnosis, especially when favorably located. Also consider surgery for recurrent hemorrhages (rupture has been reported even after normal angiography) or medically intractable seizures. Stereotactic radiosurgery has not had a satisfactorily high enough benefit to risk ratio even in symptomatic venous angiomas to justify its use[39].

31.3.1. Cavernous malformation

Key concepts:

- usually angiographically occult. May show up on MRI (open channels → flow void on T2WI, previous hemorrhage → "popcorn" pattern especially on T2* gradient echo) or contrast CT
- low-flow. No intervening neural parenchyma, no arteries. Associated with venous anomaly (represents venous outflow and should be preserved)
- presentation: usually seizures. Hemorrhage: rare, risk is difficult to predict
- treatment:
  - ◆ surgery is the treatment of choice for symptomatic accessible lesions
  - ✖ radiosurgery should not be considered as a treatment option

AKA: **cavernous hemangioma**, **cavernoma**, **cavernous angioma**, and angioma. A well circumscribed, benign vascular hamartoma consisting of irregular thick and thin walled sinusoidal vascular channels located within the brain but lacking intervening neural parenchyma, large feeding arteries, or large draining veins. Usually 1-5 cm in size. Multiple in 50% of cases[40]. May hemorrhage, calcify, or thrombose. Occur rarely in the spinal cord[41]. Caverns are filled with blood in various stages of thrombus formation/organization/dissolution. Frequently associated with venous angiomas (*see page 1104*). Capillary telangiectasias may be found adjacent to lesions and may represent a precursor. Stain positive for angiogenesis factor[42]. Lesions may arise de novo[43], and may grow (although slower than hemangioblastomas), shrink, or remain unchanged with time[44].

Pathology

Gross appearance resembles a mulberry (facetiously dubbed a "hemorrhoid

of the brain"). Light microscopy: stains for von Willebrand's factor. Smooth muscle layer is absent (except for some tiny portions). EM: shows abnormal gapping of the tight junctions between endothelial cells[45] (may permit leakage of blood).

Epidemiology

Cerebral cavernous malformations **(CM)** comprise 5-13% of CNS vascular malformations, and develop in 0.02-0.13% of the population (based on large autopsy[46] and MRI[47] series). 48-86% are supratentorial, 4-35% brainstem, 5-10% basal ganglia[48].

Spinal CMs: CMs rarely may occur in spinal cord. XRT appears to be a risk factor[49], (e.g. following craniospinal XRT[50] for medulloblastoma) especially for spinal CMs. 42% of patients with spinal CMs also harbor ≥ 1 intracranial CM[51].

Genetics

Two types: sporadic and hereditary. The latter may be inherited in a Mendelian autosomal dominant pattern with variable expressivity[52]. There appears to be at least 3 gene loci (*see Table 31-8*). Spontaneous mutations are possible.

Multiple lesions are more common in the familial form[47].

Table 31-8 Subtypes of CCM

	CCM1	CCM2	CCM3
locus	7q11-q22	7p15-13	3q25.2-q27
gene	KRIT1	MGC4607 (malcavernin)	PDCD10
feature	more common in hispanics		

Presentation/Natural History[53-55]

Seizures (60%), progressive neurologic deficit (50%), hemorrhage[A] (20%) (usually intraparenchymal), hydrocephalus, or as in incidental finding (over 50% in one series).

A. here, hemorrhage is defined as symptomatic, radiologically proven extralesional bleeding

Hemorrhage: Risk is not well delineated. Even the definition of hemorrhage is controversial since, by definition, all CMs have surrounding hemosiderin indicative of small leaks. Risk of significant hemorrhage is much less than with AVMs. CMs are prone to recurrent small hemorrhages that are rarely devastating. Hemorrhage rate tends to be low in cohort studies ≈ 2.6-3.1%/yr; appears higher in females (4.2%/yr) than males (0.9%/yr)[47]. Bleeding risk is not related to the size of the CM. Controversial if hemorrhage increases the risk of future bleeding: it did not in one study[47] whereas another study[56] found only a 0.6%/yr risk of bleeding in lesions without prior hemorrhage. Some CMs behave benignly after an initial hemorrhage. Others behave more malignantly with (> 2 hemorrhages) with increasingly more detrimental outcome. Pregnancy and parturition are not known to be risk factors for hemorrhage[52].

> **Σ** The bleeding rate is variable & even the criteria for what constitutes "bleeding" is controversial. Each patient appears to have their own natural history ∴ it is difficult to assign a risk of hemorrhage for any individual patient.

Seizures: The rate of new-seizure onset is 2.4%/yr[47].

Evaluation

CT: Not sensitive: CT misses many small lesions, some large ones, and even some that have bled. Not specific: CT findings may overlap with low grade tumors, hemorrhages, granulomas.

MRI: Gradient-echo T2WI MRI is the most sensitive test due to high sensitivity to susceptibility artifact. Findings are similar to AOVM in general (mixed signal core with low signal rim - sometimes described as "popcorn" pattern (*see above*)). The diagnosis is strongly suggested by finding multiple lesions with these characteristics and a positive family history[40]. A venous malformation may be seen adjacent to a solitary CM, but not with multiple CMs[57]. Diffusion tensor imaging/white matter tractography[58] and pre-op 3D-constructive interference in steady-state (CISS) MRI[59] may improve localization, approach, and post-op outcomes.

Angiography: Does not demonstrate lesion. MRI appearance is nearly pathognomonic, and angiography is not necessary in classically appearing cases. Angiography may be needed to R/O other diagnoses in questionable cases.

Treatment/management

Options:

1. observe
2. surgical excision
3. XRT or stereotactic radiosurgery[60-63]. Controversial: results appear comparable to natural history

No randomized prospective study has been done. Determining treatment response is difficult since no imaging study can prove elimination of the lesion. Therefore it has been suggested that *recurrent hemorrhage rate* be followed as an endpoint.

Recommendations

Incidental lesions: Asymptomatic, incidentally discovered CMs should be managed expectantly with serial imaging studies for about 2-3 years (to rule-out frequent subclinical bleeds); additional studies thereafter based on clinical grounds. However, some experts recommend removal for single, easily accessible incidental CMs in non-eloquent brain[64]. ✖ Since the radiographic appearance is almost pathognomonic, biopsy or excision solely to verify the diagnosis is rarely appropriate.

Surgery: Indications for surgery for intracranial CMs:

1. accessible lesions with
   - A. focal deficit
   - B. or symptomatic hemorrhage
   - C. or seizures:
     1. new onset seizures: there is a suggestion that removing CMs before “kindling” (*see page 396*) occurs may have a better chance of preventing future seizures
     2. difficult to manage seizures
2. less accessible lesions that repeatedly bleed with progressive neurologic deterioration may be considered for excision, even in delicate regions such as the brain stem[65-67] or spinal cord

Stereotactic radiosurgery (SRS): Some non-controlled studies have shown a possible reduction in recurrent *hemorrhage rate* following a 2 year latency period after SRS[63], however, radiation induced morbidity was significant[68, 69]. Other series have failed to show reduction[70]. Findings may reflect the natural history of CMs with temporal clustering of hemorrhagic events with decrease in

hemorrhage rates after 28 months[71].

Σ | SRS is not an alternative to surgery and should not be considered for the treatment of CMs.

Familial considerations: First degree relatives of patients with more than one family member having a cavernous malformation should have MRI screening and appropriate genetic counselling.

Surgical technique

Goal of surgery: complete removal of the malformation. Since CMs are not particularly bloody, piecemeal excision is an option; especially important in brainstem lesions.

Stereotactic localization or intraoperative ultrasound may be particularly helpful in localizing. When operating on CMs that have bled, one usually encounters a cavity containing the CM and blood degradation products[72]. Initial dissection is directed at separating the lesion from the adjacent brain. Although bleeding is usually not a problem, it occasionally may be brisk if the CM is entered before the dissection and devascularization is complete. Once the dissection is complete, the contents of the CM capsule may be removed piecemeal to minimize the parenchymal opening (especially important in the brainstem). For supratentorial CMs presenting with seizures, it is desirable to also remove the hemosiderin-stained brain immediately surrounding the CM.

Keep in mind the relatively common association of CMs with venous angiomas (see *Venous angiomas*, page 1104), which if encountered should not be removed as they represent the venous drainage of the area.

Follow-up MRI ≈ 3 months post-op is recommended. It never looks "normal" but can determine if removal was complete.

Brainstem CMs: Surgery is almost never indicated for brainstem CMs that have not bled. With a bleed rate of 2-6%, Gross et. al[73] suggest operative management for a history of > 2 prior hemorrhages and "pial/ependymal representation" on T1WI MRI.

Bleeds that do not come to the surface cannot be removed without creating neurologic deficit (worsening of neurologic outcome was 9% vs. 29% in superficial vs. deep brainstem CM resections, respectively[74]). The approach is chosen to expose the site where the bleed comes closest to the surface. Spetzler says brainstem CMs are almost always associated with a venous angioma (which, again, must be preserved since it provides the venous outflow (*see page*

1104)). Outcome was worse with surgery through the floor of the 4th ventricle than with a lateral approach. Significant short-term neurologic deficit is expected with brainstem CM resection[73].

The use of retractors is to be avoided; cottonoids and exploitation of hematoma cavity may be used to gain access. Brainstem CMs may be extremely adherent to brain parenchyma[67] unlike supratentorial CMs. Bipolar cautery: use on low power with constant irrigation to reduce thermal injury. Unlike supratentorial CMs with seizures (where you want to remove adjacent hemosiderin-stained brain), just remove the CM itself.

Spinal cord CMs: Managed essentially the same as brainstem CMs.

Cranial nerve CMs: Many case reports and reviews document CMs of cranial nerves (rarely extra-axial) with various presentations[75-77]. Case reports suggest patients may benefit from early decompression from hemorrhagic chiasmal cavernomas since they are at risk for recurrent micro-hemorrhages[78].

Prognosis

When CMs can be completely removed, the risk of further growth or hemorrhage is essentially permanently eliminated[72] (however, recurrence of symptoms has been reported after partial and even seemingly-complete removal[67, 79]).

For CMs treated surgically, patients need to be aware that post-op neurologic worsening is very common, especially with brainstem CMs[80]. Worsening may be transient[81], but may take months to resolve.

31.4. Dural AVM

Dural AVMs **(DAVM)** AKA dural arteriovenous fistula. Vascular abnormality in which an arteriovenous shunt is contained within the leaflets of the dura mater, exclusively supplied by branches of the carotid or vertebral arteries before they penetrate the dura[82]. Not true AVMs in the usual sense; qualify more as direct fistulas (*see page 1098*). May be multiple.

Usually found adjacent to dural venous sinuses. Common locations:

1. transverse (lateral) sinus: the most common[83] (63% of cases) with a slight left-sided predominance[84], with the epicenter of these almost invariably at

the junction of the transverse and sigmoid sinuses
2. in the tentorium
3. from posterior cavernous sinus, supplied by the meningohypophyseal trunk. Usually drains to junction of transverse and sigmoid sinuses, or to either one of these sinuses individually but almost never more than 1 cm from the junction
4. supplied by posterior meningeal branch of the vertebral artery

Epidemiology

DAVMs comprise 10-15% of all intracranial AVMs[84]. 61-66% occur in females, and patients are usually in their 40's or 50's. They occur rarely in children, and when they do they tend to be complex and bilateral.

Etiology

Evidence suggests that DAVMs of the transverse-sigmoid sinus junction are not congenital but are acquired lesions, resulting from collateral revascularization following thrombosis of a venous sinus[85] (often sigmoid sinus occlusion, possibly from chronic infection or trauma). The occipital artery is the dominant feeder in most cases.

Presentation

Common findings are listed in *Table 31-9*. Visual impairment included obscuration, and two patients that were blind from chronically elevated ICP. Dural sinus hypertension can produce IC-HTN by impeding cerebral venous drainage and by impairing the function of the arachnoid granulations (which can also lead to hydrocephalus). The risk of bleeding is less than with parenchymal AVMs. DAVMs may also be asymptomatic (e.g. cavernous sinus DAVMs rarely cause symptoms). Occasionally a patient may present with findings consistent with dementia.

Table 31-9 Clinical findings in 27 patients with dural AVMs[85]

Sign/symptom	No. (%)
pulsatile tinnitus	25 (92%)
occipital bruit	24 (89%)
headache	11 (41%)
visual impairment	9 (33%)
papilledema	7 (26%)

EVALUATION

MRI is usually normal.

Cerebral angiography is the diagnostic test of choice.

Angiographic classification

There are several classification systems in use. The Cognard et al. classification[A] is based on angiographic patterns and is shown in *Table 31-10*[86]. 54% had no cortical venous reflux (Types I and IIa) and usually exhibit benign behavior. There is a 2-4% chance that a low risk lesion can transform into a high risk lesion.

★ Key determinant: in this system, the pattern of venous drainage is the most critical factor. As a general rule, lesions with retrograde flow in the cortical veins (IIb, III & IV - blue squares in *Table 31-10*) are high risk (for bleeding or intracranial hypertension).

A. the Cognard system is generally more applicable to DAVMs involving the transverse sinus

MANAGEMENT

General points:

Types I & IIa: follow asymptomatic lesions, e.g. with annual Doppler studies.

Types III-V: partial occlusion does not offer protection.

A change in a bruit (either worsening, or disappearance) should prompt restudy.

Indications for intervention:

1. neurologic dysfunction
2. hemorrhage
3. refractory symptoms

Manual carotid self compression

Advocated by some, the thrombosis rate of ≈ 22% and clinical improvement rate of 33%[87] may mimic the natural course. Patients are advised to compress with the hand that would be affected by ischemia if it were to occur (e.g. with a

left-sided DAVM, the right hand should be used to compress the left carotid artery). That way, the hand would fall away if ischemia develops. Recommendations vary, one option: start with 10 minutes once a day, gradually increase frequency and duration.

Endovascular embolization

May be performed transarterial or transvenous. Before the availability of Onyx, treatment was directed at the venous drainage (unlike pial AVMs) which had higher success but also complication rates. Glue (e.g. Hystoacril or Onyx), detachable coils, or a combination have been used. For the treatment to be complete, external carotid injections must demonstrate no abnormal AV shunting. Most DAVMs are better treated endovascularly, however ethmoidal DAVMs are probably best treated microsurgically.

Surgery

Preoperative embolization by an interventional neuroradiologist will usually facilitate surgical treatment[88]. The literature is rife with warnings about rapid blood loss that frequently occurs during surgery for these lesions (including just incising the scalp), with one report of 8 units lost in 4 minutes following elevation of the bone flap[85]. Thus, the use of the craniotome is discouraged, as a sinus or venous laceration could produce a fatal hemorrhage. Contingencies for the rapid administration of blood products must be made (large bore central lines).

Patients were operated in either the semi-prone position, or supine with maximal head rotation. Lumbar spinal drainage catheters were used. A question-mark scalp incision based just behind the ear is used. Extra care is taken to place copious dural tack-up sutures to obliterate the epidural space which is abnormally vascular.

* those in bold blue boxes are high risk for bleeding or intracranial hypertension (IC-HTN)
† despite a usually good prognosis, ≈ 2% will progress and therefore follow-up studies may be warranted
‡ dashed arrows signify retrograde flow

Stereotactic radiosurgery

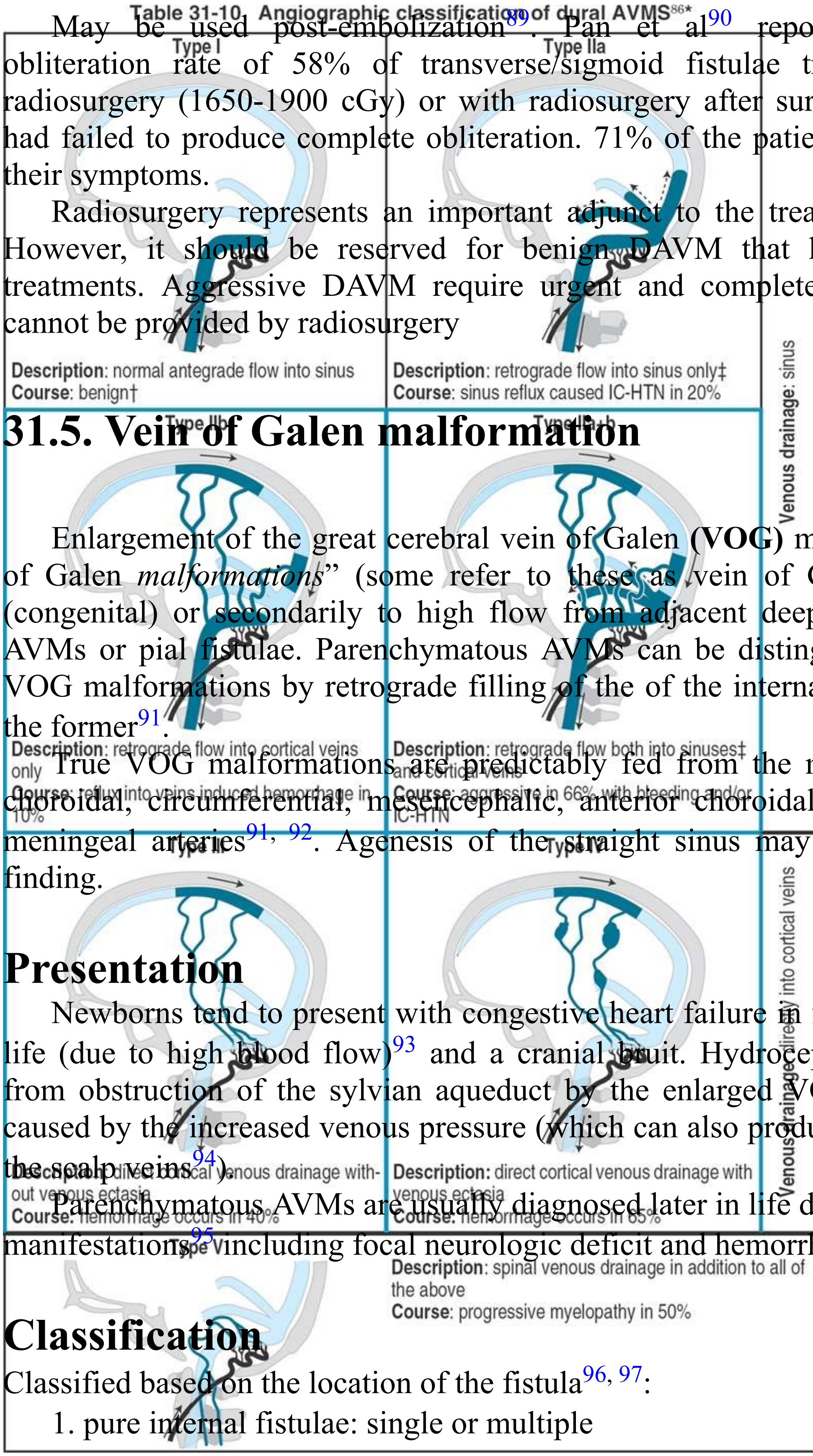

Table 31-10 Angiographic classification of dural AVMS[86]*

May be used post-embolization[89]. Pan et al[90] reported a complete obliteration rate of 58% of transverse/sigmoid fistulae treated with only radiosurgery (1650-1900 cGy) or with radiosurgery after surgery/embolization had failed to produce complete obliteration. 71% of the patients were cured of their symptoms.

Radiosurgery represents an important adjunct to the treatment of DAVM. However, it should be reserved for benign DAVM that have failed other treatments. Aggressive DAVM require urgent and complete obliteration that cannot be provided by radiosurgery

31.5. Vein of Galen malformation

Enlargement of the great cerebral vein of Galen **(VOG)** may occur in "vein of Galen *malformations*" (some refer to these as vein of Galen aneurysms) (congenital) or secondarily to high flow from adjacent deep parenchymatous AVMs or pial fistulae. Parenchymatous AVMs can be distinguished from true VOG malformations by retrograde filling of the of the internal cerebral vein in the former[91].

True VOG malformations are predictably fed from the medial and lateral choroidal, circumferential, mesencephalic, anterior choroidal, pericallosal and meningeal arteries[91, 92]. Agenesis of the straight sinus may be an associated finding.

Presentation

Newborns tend to present with congestive heart failure in first few weeks of life (due to high blood flow)[93] and a cranial bruit. Hydrocephalus may result from obstruction of the sylvian aqueduct by the enlarged VOG, or it may be caused by the increased venous pressure (which can also produce prominence of the scalp veins[94]).

Parenchymatous AVMs are usually diagnosed later in life due to neurological manifestations[95] including focal neurologic deficit and hemorrhage.

Classification

Classified based on the location of the fistula[96, 97]:

1. pure internal fistulae: single or multiple

2. fistulae between thalamoperforators and the VOG
3. mixed form: the most common
4. plexiform AVMs

Natural history

Untreated VOG malformations have a poor prognosis, with neonates having nearly 100% mortality, and 1-12 month olds having ≈ 60% mortality, 7% major morbidity, and 21% being normal[98].

Parenchymatous AVMs behave similar to other AVMs.

Treatment

Vein of Galen malformations: Pediatric patients are often in poor medical condition, limiting the efficacy of operative treatment. Treatment options for these include embolization of the main feeding arteries. Prognosis is poor. Those presenting with hydrocephalus from aqueductal obstruction often do so at the end of the first year of life. Neurosurgical excision may be considered here, and the prognosis is better.

Parenchymatous AVM with enlarged VOG: The AVM is treated by the same methods as other AVMs (embolization, resection or radiosurgery).

31.6. Carotid-cavernous fistula

Key concepts:

> - direct (high flow, from ICA) or indirect (low flow, from meningeal branches)
> - classic triad (more common with direct CCF): chemosis, pulsatile proptosis, ocular bruit
> - risk of SAH is low. Major risk is to vision
> - natural history of low flow CCF is up to 50% spontaneous thrombosis

For anatomy and venous inflow and outflow of the cavernous sinus, *see page 105*.

Carotid-cavernous fistula **(CCF)**: divided into direct (Type A) and indirect

(Types B-D)[99]:

- Type A: **direct** high-flow shunts between the internal carotid artery and cavernous sinus:
  - traumatic (including iatrogenic): occur in 0.2% of patients with craniocerebral trauma. Iatrogenic: may follow percutaneous trigeminal rhizotomy[100], endovascular procedures…
  - spontaneous: usually due to ruptured cavernous sinus ICA aneurysm. May also occur in patients with connective tissue disorders
- **indirect** (dural): most are shunts: from dural arteries that are branches of the external carotid (not from ICA) (exception: Type B) - low flow

  Type B: from meningeal branches of the internal carotid artery (ICA)
  Type C: from meningeal branches of the external carotid artery (ECA)
  Type D: from meningeal branches of both the ICA and ECA

PRESENTATION

1. orbital and/or retro-orbital pain
2. chemosis (arteriolization of conjunctiva)
3. pulsatile proptosis
4. ocular and/or cranial bruit
5. deterioration of visual acuity: may be due to hypoxic retinopathy as a result of reduced arterial pressure and increased venous pressure and increased intraocular pressure
6. diplopia: abducens (VI) palsy is the most common
7. pupillary dilatation
8. ophthalmoplegia (usually unilateral, but may present initially as bilateral or may progress to bilateral)
9. increased intraocular pressure
10. neo-vascularization of the iris or retina
11. rarely: SAH

Indirect CCFs generally have a more gradual onset and milder presentation than direct.

EVALUATION

CT or MRI: usually demonstrates proptosis. Serpiginous and engorged intraocular vessels including the superior ophthalmic vein (best seen on T2WI coronals - helps to differentiate from rectus muscles) and convexity of lateral

wall of cavernous sinus.

Angiography: shunting of blood from ICA into cavernous sinus. Rapid opacification of petrosal sinus and/or ophthalmic vein may be seen.

1. Huber maneuver: lateral view, inject VA and manually compress affected carotid. Helps identify upper extent of fistula, multiple fistulous openings, and complete transection of ICA
2. Mehringer-Hieshima maneuver: inject contrast at a rate of 2-3 ml/s into affected carotid while compressing the carotid in the neck (below the catheter tip) to control flow to help demonstrate the fistula

TREATMENT

20-50% of <u>low flow</u> CCF spontaneously thrombose, therefore one may observe these as long as visual acuity is stable and intraocular pressure is $< \approx 25$. Symptomatic (e.g. progressive visual deterioration) high-flow CCFs rarely resolve spontaneously, and urgent treatment is usually indicated. Treatment is usually in the form of embolization by an interventional neuroradiologist or trapping between surgically placed clips.

Even if normal ocular motility cannot be achieved in affected eye, preservation of vision is desirable because:

1. for some motility abnormalities, surgical treatment may reduce diplopia
2. patient may be provided with frosted eyeglass lens which will eliminate diplopia but will maintain peripheral vision
3. in the rare event of injury to contralateral eye (trauma, central retinal artery occlusion…) there would be "reserve" vision in the eye with reduced motility (with loss of the other eye, there would not be diplopia)

Indications for treatment:

1. proptosis
2. visual loss
3. cranial nerve VI palsy
4. intractable bruit
5. severely elevated intraocular pressure
6. increased filling of cortical veins on angiography

ENDOVASCULAR TREATMENT

Options include:

1. electrolytically detachable coils

2. Amplatzer vascular plug

Routes available include:

1. transarterial through internal carotid. If this fails (e.g. wide aneurysm neck), the carotid artery may be occluded on either side of fistula to trap it (sacrifices carotid artery, therefore test occlusion must be done first[A] to determine if patient can tolerate this). The distal occlusion needs to be proximal to the ophthalmic artery
2. transarterial through external carotid: useful only for dural fistulas
3. transvenous:
    A. traversing heart to enter jugular vein, then through petrosal sinus to cavernous sinus. Lower success rate (≈ 20%) than transarterial route
    B. via superior ophthalmic vein: entered where supra-optic vein enters orbit to become superior ophthalmic vein. If possible, it is best to wait for the vein to become arterialized by the high flow pressure. Reports of "disasters" due to injury to the fragile vein performed before arteriolization took place may have been due to more primitive balloon catheters that were standard before current commercially produced versions were available (which are softer than original). Must avoid lacerating the vein inside the orbit, and avoid distal ligation of the vein without proximal occlusion (shunts even more blood into eye)

A. test occlusion with an open fistula may give false positive result because steal through the fistula may reduce CBF and cause neurologic symptoms not related to the occlusion acting alone

Choice of technique

With indirect fistulas, it is mandatory to place coils on the venous side (otherwise new feeders will be recruited).

Coils of clips may be used to occlude direct fistulas.

31.7. References

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NOTES

32. Intracerebral hemorrhage

Intracerebral hemorrhage **(ICH)** is a hemorrhage within the brain parenchyma. Formerly commonly referred to as "**hypertensive hemorrhage**", but hypertension is a debatable etiology in many cases (see *Hypertension as a cause?*, page 1122).

32.1. Intracerebral hemorrhage in adults

Key concepts:

- the second most common form of stroke (15-30% of strokes), but the most deadly
- unlike ischemic infarct: smooth progressive onset over minutes to hours, often with severe headache, vomiting and alterations in level of consciousness
- unenhanced CT scan of the brain is the initial diagnostic study of choice
- the volume of the hematoma correlates highly with morbidity and mortality
- the clot enlarges in at least 33% of cases within the first 3 hours of onset
- angiography is recommended (as long as it doesn't delay emergent treatment) except for patients > 45 yrs of age with preexisting hypertension and ICH in thalamus, putamen or posterior fossa
- treatment
  - still controversial. The initial promise of rFVIIa has not been actualized
  - the usefulness of surgery is still controversial, but seems limited to some cerebellar hemorrhages and select supratentorial hemorrhages that come within 1 cm of the cortical surface

EPIDEMIOLOGY

INCIDENCE

The second most common form of stroke (≈ 15-30% of all strokes, and the

most deadly. Approximately 12-15 cases per 100,000/yr. Approximately twice the incidence as SAH[1]. Onset is usually during activity (rarely during sleep), which may be related to elevation of BP or increased CBF (see *Etiologies* below).

Table 32-1 Relative risk of ICH with EtOH consumption

Period prior to ICH	Amount* (g EtOH)	Relative risk
24 hours	41-120	4.6
	> 120	11.3
1 week	1-150	2.0
	151-300	4.3
	> 300	6.5

* 1 standard drink = 12 g EtOH

Risk factors

The following are epidemiologic risk factors, also see *Etiologies*, page 1119 for others.

1. age: the incidence increases significantly after age 55 years and doubles with each decade of age until age > 80 yrs where incidence is 25 times that during previous decade. Relative risk for age > 70 yrs is 7
2. gender: more common in men
3. race: in the U.S., ICH affects blacks more than whites. May be related to higher prevalence of HTN in blacks. Incidence may also be higher in orientals[2]
4. previous CVA (any type) increases risk to 23:1
5. alcohol consumption[2, 3]:
   A. recent use: moderate or heavy alcohol consumption both within the 24 hours and the week preceding the ICH were risk factors for ICH[4] as shown in *Table 32-1*
   B. chronic use: one study suggests that consuming > 3 drinks a day increases the risk of ICH by ≈ 7 times[5 (p 15)]
   C. ICH in patients with high ethanol consumption were more commonly lobar[6]
6. cigarette smoking: does <u>not</u> increase the risk of ICH[7, 8]
7. street drugs: cocaine, amphetamines, phencyclidine[9]

8. liver dysfunction: hemostasis may be impaired on the basis of thrombocytopenia, reduced coagulation factors, and hyperfibrinolysis[10]

LOCATIONS OF HEMORRHAGE

Common sites of ICH are shown in *Table 32-2*. Common arterial feeders of ICHs:

- lenticulostriates: the source of putaminal hemorrhages (possibly secondary to microaneurysms of Charcot-Bouchard, *see below*)
- thalamoperforators
- paramedian branches of BA

Table 32-2 Common sites for ICH (modified[11])

%	Location
50%	striate body (basal ganglia); putamen most common; also includes: lenticular nucleus, internal capsule, globus pallidus
15%	thalamus
10-15%	pons (≈90% of these are hypertensive)
10%	cerebellum
10-20%	cerebral white matter
1-6%	brain stem

Lobar hemorrhage

Incorporates primary hemorrhages into the occipital, temporal, frontal and parietal lobes (including ICH arising from cortex and subcortical white matter), as opposed to hemorrhage of deep structures (e.g. basal ganglion, thalamus, and infratentorial structures)[12]. Accounts for 10-32% of nontraumatic ICHs[12]. With large hemorrhages, it may be difficult to make a distinction between lobar and deep ICH.

Lobar hemorrhages are more likely to be associated with structural abnormalities than deep hemorrhages (*see below*). They may also be more common in patients with high alcohol consumption (*see above*). Lobar hemorrhages may also have a more benign outcome than ganglionic-thalamic hemorrhages[12].

Etiologies: Although many causes of ICH can produce lobar hemorrhages (*see below* for a detailed list), those that are more likely to produce lobar

hemorrhages include:

1. extension of a deep hemorrhage
2. cerebral amyloid angiopathy: the most common cause of lobar ICH in elderly normotensive patients (*see page 1122*)
3. trauma
4. hemorrhagic transformation of an ischemic infarct: *see below*
5. tumor: *see page 1123*. Multiple lobar hemorrhages may occur with metastases
6. cerebrovascular malformation (especially AVM): *see page 1098*
7. rupture of an aneurysm: *see below* for circumstances likely to produce this
8. idiopathic

Internal capsule

There may be prognostic significance with regard to contralateral motor function if the hemorrhage is medial to and/or extending through the internal capsule **(IC)**, or lateral to the IC and merely compressing it, making the clot more accessible to surgical treatment without damaging the IC.

ETIOLOGIES

History check list

Based on information in this section, the following check-list is presented to assist in the gathering of historical information important in evaluating the adult with ICH:

❏ 1. hypertension

❏ 2. drugs:
   - A. sympathomimetics:
     1. amphetamines, cocaine
     2. appetite suppressants or nasal decongestants (phenylpropanolamine, pseudoephedrine)
   - B. dietary supplements: especially ephedra alkaloids (ma huang)
   - C. anticoagulants: warfarin in particular
   - D. antiplatelet drugs: aspirin, NSAIDs, Plavix
   - E. birth control pills: questionable association

❏ 3. history of alcohol abuse

❏ 4. coagulopathies

❑ 5. leukemia
❑ 6. previous stroke
❑ 7. history of known vascular abnormalities (AVM, venous angioma…)
❑ 8. tumor: known history of cancer, especially those that tend to go to brain (lung, breast, GI, renal, melanoma…)
❑ 9. recent surgery: especially carotid endarterectomy, procedures requiring heparin…
❑ 10. recent childbirth and/or eclampsia or preeclampsia
❑ 11. history of recent trauma

Etiologies

1. "hypertension" (debatable as a cause or effect, *see below*) but is a risk factor
   A. acute hypertension **(HTN)**: as may occur in eclampsia (*see below*) or with use of certain drugs (e.g. cocaine, phenylpropanolamine…, *see page 1121*)
   B. chronic HTN: possibly causes degenerative changes within blood vessels
2. possibly associated with acutely increased CBF (globally or focally)[13], especially to areas previously rendered ischemic:
   A. following carotid endarterectomy[14, 15]
   B. following repair of congenital heart defects in children[16]
   C. previous CVA (embolic[17] or otherwise): **hemorrhagic transformation** may occur in up to 43% of CVAs during the first month[18]. May follow dislodgment or recanalization of an arterial occlusion, although it has been demonstrated with persistent occlusion[19]. May occur as early as ≤ 24 hrs after a CVA in patients with a negative CT done within 6 hours[20]. Two types[18, 21]:
      • type 1: diffuse or multifocal. Heterogeneous or mottled appearance within the boundaries of the CVA. Less hyperdense than primary ICH
      • type 2: extensive hematoma. Probably unifocal source. As hyperdense as primary ICH and may extend outside the original CVA boundaries. Unlike type 1, classically associated with anticoagulation therapy, and tends to occur in initial few days after CVA and is often associated with clinical worsening. May be difficult to distinguish from primary ICH, and may be frequently

misdiagnosed as such[20]

D. migraine: during[22] or following[23] a migraine attack (probably an exceedingly rare event)

E. following surgery to remove an AVM: "normal perfusion pressure breakthrough". Some cases may be due to incomplete AVM excision

F. physical factors: following strenuous physical exertion[24], exposure to cold[25]…

3. vascular anomalies
   A. AVM: rupture (see *Arteriovenous malformation*, page 1098)
   B. aneurysm rupture
      1. saccular ("berry") aneurysms:
         a. aneurysms of the circle of Willis **(COW)**: ICH may be more likely with aneurysms that have become adherent to brain surface by fibrosis from inflammation or previous hemorrhages. May produce ICH when they rupture instead of the usual SAH
         b. aneurysms distal to the COW (e.g. MCA aneurysms)
      2. microaneurysms of **Charcot-Bouchard**: *see below*
   C. venous angioma rupture
4. "arteriopathies"
   A. amyloid angiopathy: usually → repeated lobar hemorrhages (*see below*)
   B. fibrinoid necrosis[26, 27] (sometimes seen in cases of amyloid angiopathy)
   C. **lipohyalinosis**: subintimal lipid-rich hyaline material[28]
   D. cerebral arteritis (including necrotizing angiitis)
5. brain tumor (primary or met): see *Hemorrhagic brain tumors* below
6. coagulation or clotting disorders
   A. iatrogenic
      1. patients receiving anticoagulation therapy: *see page 1123*
      2. thrombolytic therapy:
         a. for acute ischemic CVA: incidence of symptomatic ICH within 36 hrs of treatment with rtPA is 6.4% (vs. 0.6% in the placebo treated group)[29] (*see page 1017*)
         b. for acute MI or other thrombosis: incidence is ≈ 0.36-2%[30-32]. Risk is increased with higher doses than the recommended 100 mg of alteplase (Activase®, recombinant tissue plasminogen activator **(rt-PA)**)[33], in older patients, in those with anterior MI

or higher Killip class, and with bolus administration (vs. infusion)[34]. When heparin was used adjunctively, higher doses were associated with higher risk of ICH[35]. ICH is thought to occur in those patients with some preexisting underlying vascular abnormality[36]. Immediate coronary angioplasty is safer than rtPA when available[32]

3. aspirin:
   a. one ASA qod was associated with increased risk of ICH[37], with a rate of 0.2-0.8% per year[38]
   b. ASA 100 mg/d did not increase the risk of significant ICH in patients > 60 yrs with mild to moderate head injury (GCS ≥ 9)[39]

B. leukemia

C. thrombocytopenia:
   1. thrombotic thrombocytopenic purpura
   2. aplastic anemia

7. CNS infection:
   A. especially fungal, which attack blood vessels
   B. granulomas
   C. herpes simplex encephalitis: may initially produce low density lesions that progress to hemorrhagic ones
8. venous or dural sinus thrombosis: *see page 1166*
9. drug related
   A. substance abuse
      1. alcohol: > 3 drinks/day increases the risk of ICH ≈ 7-fold (*see page 1118*)
      2. drug abuse: especially sympathomimetics (cocaine[40, 41], amphetamine[42]
   B. drugs that raise BP:
      1. alpha-adrenergic agonists (sympathomimetics): phenylpropanolamine[43, 44] (may also cause ischemic CVA, *see page 1025*) which was removed from OTC nasal decongestants and appetite suppressants, but other OTC alpha agonists (including phenylephrine, ephedrine[45], and pseudoephedrine[46]) are also problematic[47]
      2. ephedra alkaloids: sold as a dietary supplement (ma huang) to suppress appetite and increase energy. Associated in <u>case reports</u> with HTN, SAH, ICH, seizures and death[48]

10. post-traumatic: often in a delayed fashion[49, 50] (see *Hemorrhagic contusion*, page 893)
11. pregnancy related: the risk of ICH in pregnancy and puerperium (up to 6 weeks post partum) is ≈ 1 in 9,500 births[51]
    A. most commonly associated with eclampsia or preeclampsia: the mortality of eclampsia is ≈ 6% with ICH being the most frequent direct cause[52] (also see *Pregnancy & intracranial hemorrhage*, page 1086)
    B. postpartum ICH (median 8 days, range 3-35 days) in the absence of eclampsia has been reported[53]; when associated with vasculopathy the term **post-partum cerebral angiopathy** has been used
    C. vascular findings:
        1. some cases associated with isolated cerebral vasculopathy in the absence of systemic vasculitis[54]
        2. some cases demonstrate vasospasm
        3. some cases show findings (e.g. patchy enhancement in occipital lobes) suggestive of cerebrovascular dysautoregulation (*see page 73*)
        4. some cases show no vascular-related abnormalities
12. post-operative:
    A. following carotid endarterectomy (*see above*)
    B. following craniotomy:
        1. at site of craniotomy[55]: risk factors identified
            a. especially within residual astrocytoma after subtotal resection
            b. following craniotomy for AVM (*see above*)
        2. at site remote from craniotomy. In a series of 37 patients, unlike hematomas at craniotomy site, the following were identified as not being related to risk of hemorrhage: HTN, coagulopathy, CSF drainage, underlying occult lesion
            a. following drainage of chronic SDH: *see page 901*
            b. cerebellar hemorrhage
                i. following pterional craniotomy[56] (this author incriminated possibly rapid overdrainage of CSF)
                ii. following temporal lobectomy[57]
13. idiopathic[12]

Cerebellar hemorrhage etiologies

Etiologies are similar to ICH of any location, however, some nuances:

1. HTN is a factor in up to two-thirds of cerebellar hemorrhages
2. AVM is a consideration, aneurysm is very rare (possibly AICA aneurysm, but usually only in association with other high-flow lesion, e.g. AVM[58])
3. may be related to recent previous spinal or supratentorial surgery

Hypertension as a cause?

Hypertension **(HTN)** is controversial as cause of ICH since the incidence of both ICH and HTN increases with age (66% of patients > 65 yrs have HTN). The relative risk for ICH with HTN is 3.9-5.4, depending on the definition of HTN used[59]. Many patients with ICH are dramatically hypertensive on presentation, however, acute elevations of ICP from the hemorrhage may actually precipitate HTN (part of Cushing's triad, see *Table 27-17*, page 868). HTN is probably a risk factor primarily for pontine/cerebellar ICH and is probably not a factor in at least 35% of basal ganglion hemorrhages.

Microaneurysms of Charcot-Bouchard

AKA miliary aneurysms[60]. Occur primarily at bifurcation of small (< 300 μm) perforating branches of lateral lenticulostriate arteries in basal ganglia, more common in hypertensive patients[61]. Possibly the origin of some "hypertensive" ganglionic (putaminal) hemorrhages[62], but this is controversial.

(Cerebral) amyloid angiopathy

Cerebral amyloid angiopathy **(CAA)** AKA **congophilic angiopathy**. Pathologic deposition of beta amyloid protein (appears as birefringent "apple-green" under polarized light when stained with congo red) within the media of small meningeal and cortical vessels (especially those in white matter) without evidence of systemic amyloidosis[63]. Some vessels may show fibrinoid necrosis of vessel wall[64, 65].

CAA should be suspected in patients with recurrent hemorrhages (uncommon with "hypertensive hemorrhages"[66]) that are lobar in location (*see page 1119*). **Gradient-echo MRI** may identify petechial hemorrhages or hemosiderin deposits from small cortical hemorrhages which may be associated with CAA[67]. Less likely in the case of basal ganglion or brain stem hemorrhages[12].

Table 32-3 Criteria for the diagnosis of CAA[71]

Definite CAA	Full postmortem exam showing all 3 of the following: A. lobar, cortical, or corticosubcortical hemorrhage B. severe CAA C. absence of another diagnostic lesion
Probable CAA with supporting pathological evidence	Clinical data & pathological tissue showing all 3 of the following: A. lobar, cortical, or corticosubcortical hemorrhage B. some degree of vascular amyloid deposition in specimen C. absence of another diagnostic lesion
Probable CAA	Clinical data and MRI findings showing all 3 of the following: A. age ≥ 60 yrs B. multiple hemorrhages restricted to the lobar, cortical, or corticosubcortical region C. absence of another cause of hemorrhage*
Possible CAA	Clinical data and MRI findings: A. age ≥ 60 yrs B. single lobar, cortical, or corticosubcortical hemorrhage without another cause*, or multiple hemorrhages with a possible but not a definite cause* or with some hemorrhages in an atypical location (e.g. brain stem)

* e.g. excessive anticoagulation (INR > 3.0), head trauma, ischemic CVA, CNS tumor, cerebrovascular malformation, vasculitis or blood dyscrasia

Incidence increases with age: CAA is present in ≈ 50% of those over 70 years of age[68], however, most do not hemorrhage. CAA is probably responsible for ≈ 10% of cases of ICH. May be associated with genetic factors (including the apolipoprotein E ε4 allele[69]), and may be more prevalent in patients with Down syndrome. Although they are distinct diseases, there is some overlap between CAA and Alzheimer's disease; the amyloid in CAA is identical to that found in senile plaques of Alzheimer's disease. CAA may increase the risk of ICH by potentiating plasminogen[70] (may be of special relevance to patients receiving tissue plasminogen activator **(t-PA)** to treat MI or CVA).

Patients with CAA may present with a TIA-like prodrome (*see below*).

Among patients with lobar hemorrhage, those with the apoE ε4 allele typically have their first hemorrhage > 5 yrs earlier than noncarriers (73 ± 8 yrs vs./79 ± 7 yrs)[69].

Diagnostic tests are useful mainly to rule-out other conditions. The definitive diagnosis of CAA requires pathologic evaluation of brain tissue. Criteria for the diagnosis of CAA are shown in *Table 32-3*[71].

Hemorrhagic brain tumors

Although any brain tumor can hemorrhage, tumoral ICH is usually

associated with malignancies. Tumors can also produce SAH(*see page 1034*) or subdural hematomas.

Malignant tumors most commonly associated with ICH:

1. glioblastoma
2. lymphoma
3. metastatic tumors
   A. melanoma[72, 73]: ≈ 40% hemorrhage
   B. choriocarcinoma[72, 74, 75]: ≈ 60% hemorrhage
   C. renal cell carcinoma
   D. bronchogenic carcinoma: although only ≈ 9% hemorrhage, this tumor is such a frequent source of cerebral mets that it therefore is a more common source of tumoral ICH

Malignant tumors that hemorrhage less commonly include:

1. medulloblastoma[76-79] (most commonly in children)
2. gliomas[80, 81]

Some <u>benign</u> brain tumors that have been associated with ICH include:

1. meningiomas have been associated with intratumoral, subdural, and nearby parenchymal hemorrhage[82-85]. Tendency to bleed is similar for angioblastic variety as for other highly vascular meningiomas
2. pituitary adenoma (see *Pituitary apoplexy*, page 635)
3. oligodendroglioma (relatively benign): rarely presents with hemorrhage[86], classically after years of causing seizures
4. hemangioblastoma[87]
5. vestibular schwannoma[88-90]
6. cerebellar astrocytoma[91]

Anticoagulation preceding ICH

10% of patients on warfarin develop a significant bleeding complication per year, including ICH (65% mortality in this group). The risk of ICH in patients treated with warfarin for A-fib varies between 0-0.3% per year[38] (historically, this was as high as ≈ 1.8% in older studies[92] from the 1960's and 70's), but when an elderly subgroup (mean age 80 yrs) was analyzed, this rate was 1.8% per year[38]. ICH was the only cause of fatal bleeding complications of warfarin therapy in one series where the cumulative risk of a fatal hemorrhage was 1% at

1 year and 2% at 3 yrs[93].

The risk of hemorrhagic complications was increased with the length and also the variability of the PT, and during the first three months of anticoagulation[93]. Patients with cerebral amyloid angiopathy **(CAA)** (*see above*) are also at increased risk of ICH following administration of antiplatelet drugs or anticoagulants[71].

CLINICAL

In general, the neurologic deficit with ICH is characterized by a smooth progressive onset over minutes to hours, unlike embolic/ischemic CVA where deficit is maximal at onset. With ICH, severe headache, vomiting and alterations in level of consciousness may be more common (H/A may not be more prevalent than in embolic CVA, but it is often a first and prominent symptom[12]).

Prodrome

TIA-like symptoms may precede lobar hemorrhages[94, 95] in patients with CAA, and may occur in up to ≈ 50% of patients for whom a complete history is obtainable. Unlike typical TIAs, these usually consist of numbness, tingling or weakness (involving the area where the hemorrhage will subsequently occur) that gradually spreads in a manner reminiscent of a Jacksonian-march and may spill-over vascular territories (probably an electrical phenomenon rather than an ischemic event). This is suggestive of but not pathognomonic for the subsequent development of lobar ICH.

CONCOMITANTS OF SPECIFIC LESIONS IN ICH

Putaminal hemorrhage

The most common site for ICH. Smooth gradual deterioration in 62% (maximal deficit at onset in 30%); never fluctuating. Contralateral hemiparesis, may progress to hemiplegia or even coma or death. H/A in 14% at onset. No H/A at any time in 72%. Papilledema and **subhyaloid preretinal hemorrhage** are rare.

Thalamic hemorrhage

Classically, contralateral hemisensory loss. Also hemiparesis when the internal capsule is involved. Extension into upper brain stem → vertical gaze

palsy, retraction nystagmus, skew deviation, loss of convergence, ptosis, miosis, anisocoria, ± unreactive pupils. H/A in 20-40%. Motor deficit similar to putaminal hemorrhage, but contralateral sensory deficit widespread and striking. Hydrocephalus may occur from compression of CSF pathways.

In 41 patients, when hemorrhage > 3.3 cm on CT, all died. Smaller hematomas usually caused permanent disability.

Cerebellar hemorrhage

May include any combination of the following:

1. symptoms of increased ICP (lethargy, N/V, HTN with bradycardia…) due to hydrocephalus which may occur as a result of:
   A. compression of the 4th ventricle → obstruction of CSF
   B. extension of the hemorrhage into the ventricular system
2. direct compression of brain stem may produce:
   A. facial palsy: due to pressure on the facial colliculus
   B. these patients classically become comatose without first having hemiparesis, unlike many supratentorial etiologies

Lobar hemorrhage

Syndromes associated with hemorrhage in the 4 cerebral lobes[12] (≈ 50% have H/A):

1. frontal lobe (the most distinctive of the syndromes): frontal H/A with contralateral hemiparesis, usually in the arm with mild leg and facial weakness
2. parietal lobe: contralateral hemisensory deficit and mild hemiparesis
3. occipital lobe: ipsilateral eye pain and contralateral homonymous hemianopsia, some may spare superior quadrant
4. temporal lobe: on dominant side, produces fluent dysphasia with poor auditory comprehension but relatively good repetition

Delayed deterioration

Deterioration after the initial hemorrhage is usually due to any combination of:

1. rebleeding: *see below*
2. edema: *see below*
3. hydrocephalus: higher risk with intraventricular extension or posterior fossa ICH

4. seizures

Rebleeding or extension of bleed

Early rebleeding: Rebleeding (more so in basal ganglion hemorrhages than in lobar hemorrhages) has been documented during the first hour by "ultra-early" scanning and repeating CT scans. Rebleeding is usually accompanied by clinical deterioration[96]. The incidence of hematoma enlargement decreases with time, 33-38% in 1-3 hours[97], 16% in 3-6 hrs, and 14% between 24 hrs of onset and a second CT within 24 hrs of the first[98]. Patients with enlarging hematomas were more likely to have larger hematomas and/or coagulopathy, and had a worse outcome[98]. Rebleeding may still occur following surgical evacuation of clot even with satisfactory intraoperative hemostasis. Hemostatic agents (e.g. NovoSeven®) may reduce this risk, *see page 1127*. The "**spot sign**"[99] on CTA (small enhancing foci within acute ICH) correlated with increased risk of hematoma expansion.

Late rebleeding: Quoted rates for late rebleeding from ICH range from 1.8–5.3% (depending on length of follow-up)[100]. Diastolic BP was significantly higher in the group with recurrent hemorrhage, with a 10%/yr risk for DBP > 90 mm Hg vs. < 1.5% for DBP ≤ 90 (mean F/U of 67 months)[100]. Other risk factors include diabetes and tobacco and alcohol abuse[101]. Recurrent hemorrhages may indicate underlying vascular malformations or amyloid angiopathy (lobar rebleeding is likely to be due to amyloid angiopathy[101]).

Edema

Edema and ischemic necrosis around the hemorrhage may cause delayed deterioration[26]. Although necrosis from mass effect of the clot contributes a small part to the edema, by itself, the mass effect is insufficient to account for the amount of edema that occurs. It is believed that an edemogenic toxin is released from the clot. Experiments with various components of blood clots has disclosed that thrombin in concentrations that could be released from the clot causes increased permeability of the blood-brain-barrier, and is also a potent vasoconstrictor. This is the leading suspect as the major cause of delayed edema and deterioration. Also see *Cerebral edema*, page 109.

EVALUATION

CT SCAN

CT scan is rapid, and easily demonstrates blood as high density within the brain parenchyma immediately after hemorrhage. Although mass effect is common, the tendency for the hemorrhage to dissect through brain tissue often results in less mass effect than would be anticipated from the size of the clot.

Clot volume carries prognostic significance (*see page 1129*). It can be measured volumetrically using computer algorithms available in some CT scanners, or it can very simply be approximated by the **ellipsoid method**[102] (originally developed for AVMs, based on the principal that the volume of an ellipsoid is approximately half of that of a parallelepiped into which it is placed)[103] and is simpler than other slightly more accurate estimation methods[104] as shown in *Eq 32-1*, where AP, LAT and HT are the diameters of the clot in each of the 3 dimensions (antero-posterior, lateral, and height[A]).

$$\boxed{\text{ellipsoid volume} \approx \frac{AP \times LAT \times HT}{2}} \qquad \textbf{Eq 32-1}$$

A. to estimate height of a lesion when only axial images are available (as on most initial CTs), count the number of images on which the lesion is seen, and multiply by the slice thickness of the CT cuts[102, 104, 105] (this information is usually printed on the CT), or, subtract the table position (usually printed on CT) of the highest cut that shows the clot from the table position of the lowest cut showing clot

On the average, the size of the clot decreases ≈ 0.75 mm/day, and the density decreases by ≈ 2 CT units/day, with little change for 1st 2 wks.

MRI

Usually not the procedure of choice for initial study. Does not show blood well within the first few hours. Difficult to ventilate or access patient during the study. Slower and more expensive than CT. May be useful later, e.g. to help diagnose cerebral amyloid angiopathy **(CAA)** (*see page 1122*).

The appearance of ICH on MRI is very complicated. It is highly dependent on the age of the clot[106] with 5 stages identified (*see Table 32-4*).

Table 32-4 Variation of MRI appearance of ICH with time since hemorrhage*[106]

Stage	Age	Condition of hemoglobin	T1WI	T2WI
hyper-acute	< 24 hrs	oxy-Hgb (intracellular)	iso	sl. ↑
acute	1-3 d	deoxy-Hgb (intracellular)	sl. ↓	very ↓
subacute				
• early	> 3 d	met-Hgb (intracellular)	very ↑	very ↓
• late	> 7 d	met-Hgb (extracellular†)	very ↑	very ↑
chronic				
• center	> 14 d	hemichromes‡ (extracellular)	iso	sl. ↑
• rim		hemosiderin (intracellular)	sl. ↓	very ↓

* Abbreviations: oxy-Hgb = oxyhemoglobin, deoxy-Hgb = deoxy-hemoglobin, met-Hgb =methemoglobin, iso = iso-intense to brain, ↓ = hypo-intense, ↑ = hyperintense, sl = slightly

† when the RBCs lyse, the Hgb becomes extracellular

‡ diamagnetic (non-paramagnetic) heme derivatives

Cerebral angiography

For making the diagnosis of the ICH itself, angiography cannot reliably differentiate the mass effect from an ICH from that due to an ischemic infarct or tumor[107]. May demonstrate AVMs and aneurysms when they are associated with the ICH. The yield may be increased by delaying the study[12]. May demonstrate vascular blush in some cases of tumor. Normal arteriography cannot eliminate cerebral amyloid angiopathy[108].

For indications for cerebral angiography in ICH, *see below*.

ICH score

The system of Hemphill et al.[109] assigns points based on 5 features as indicated in *Table 32-5*. The points are then summed for the "ICH score". The associated 30 day mortality based on the ICH score is tabulated in *Table 32-6*.

Table 32-5 ICH Score[109]

Feature	Finding	Points
GCS score (*Table 12-1*, page 279)	3-4	2
	5-12	1
	13-15	0
Age*	≥ 80 years	1
	< 80	0
Location	infratentorial	1

	supratentorial	0
ICH volume (*Eq 32-1*)	≥ 30 cc	1
	< 30 cc	0
Intraventricular blood	yes	1
	no	0
"ICH Score" = Total Points		0-6

* possible bias since treatment decisions in elderly patients may have differed from younger ones

Table 32-6 Mortality based on ICH Score

ICH Score*	30 day mortality
0	0% (26 pts)
1	13% (32 pts)
2	26% (27 pts)
3	72% (32 pts)
4	97% (29 pts)
5	100% (6 pts)
6	? 100%† (0 pts)

* from *Table 32-5*

† no pt. in the study had a score of 6, but "it is expected this would be associated with high rate of mortality"

INITIAL MANAGEMENT OF ICH

There is not uniform agreement on almost all aspects of the management of ICH from the optimal BP to the indications for surgery. The following is offered as a guide.

1. patients should be managed in an ICU
2. HTN: controversial. Issues: HTN may contribute to further bleeding, especially within the first hour[96]. However, some HTN may be needed to maintain perfusion[A]. Some say reduce MAP to pre-morbid level if known, or by ≈ 20% if unknown

Σ Treat HTN. Suggested target BP ≈ 140/90. Avoid overcorrection (relative or absolute hypotension)

3. intubate if stuporous or comatose
4. maintain euglycemia

5. maintain normothermia
6. anticonvulsants
   A. seizures are treated with appropriate AEDs
   B. prophylactic AEDs: optional. May decrease risk of early seizures in patients with lobar hemorrhages
   C. AED options
      1. Keppra has a very favorable therapeutic/toxic profile. Dose 500 mg BID
      2. phenytoin (load with 17 mg/kg slow IV over 1 hour, follow with 100 mg q 8 hrs, see *phenytoin (PHT) (Dilantin®)*, page 409)
7. hemostatic issues:
   A. check INR (or PT), PTT & platelet count **(PC)**, platelet function assay (PFA)
      1. correct coagulopathies (see *Correction of coagulopathies or reversal of anticoagulants*, page 40)
      2. platelets
         a. thrombocytopenia: although platelet transfusions are generally recommended only for PC < 50K, ICH is so serious that a suggestion is to keep PC > 75K
         b. patients on platelet inhibiting drugs (e.g. aspirin or Plavix®) should receive platelets
         c. when needed: start with 6 units of platelets (see *Platelets* on page 34)
   B. bleeding time: not generally helpful
   C. ★ hemostatic agents: NovoSeven® (recombinant activated coagulation factor VII **(rFVIIa)**) given IV within 4 hours of onset[111], *see below*
8. steroids: controversial. No benefit from dexamethasone in ICH, with significantly more complications (primarily infectious, GI bleeding and diabetogenic)[112]. Consider use if significant peri-hemorrhage edema on imaging (suggested dosage[113]: 4 mg dexamethasone IV q 6 hrs, tapered over 7-14 days)
9. treat intracranial hypertension presumptively: mannitol and/or furosemide as tolerated, also helps with HTN (for more, see *Treatment measures for elevated ICP*, page 876) If significant problems from suspected increased ICP, consider ICP monitor
10. follow electrolytes and osmolarity
    A. aggressively treat hyperglycemia (insulin drip if problematic)

B. watch for SIADH

11. **angiography**: primarily to R/O underlying vascular malformation, but also to R/O aneurysm (a less common cause of ICH), and tumor (which is usually better diagnosed on contrast CT or MRI)
   A. if urgent surgery is indicated (e.g. for herniation), the delay in obtaining an angiogram may be detrimental and it may be best deferred to post-op
   B. ★ **indications**: angiography is recommended <u>except</u> for patients > 45 yrs of age with preexisting hypertension <u>and</u> ICH in thalamus, putamen or posterior fossa due to a 0% yield out of 29 patients in this group[114] and low yield in all patients with isolated deep ICH[115]
      1. patients > 45 yrs with HTN and a <u>lobar</u> ICH: angiography had a 10% yield[114], with the ratio of AVM:aneurysm ≈ 4.3:1
      2. patients with intraventricular hemorrhage (without parenchymal hematoma): the yield of angiography was ≈ 65%[114], primarily AVM
   C. an underlying lesion may be obliterated by ICH, especially acutely. If initial angio is negative, repeat after CT shows resorption of clot (≈ in 2-3 mos). If still negative, follow CT or MRI q 4–6 mos for ≈ 1 year to R/O tumor[26]. Delaying the initial angiogram for several weeks may increase the yield and is also an option[12]
   D. MRI/MRA has ≈ 90% sensitivity for detecting structural abnormalities in this setting, and so a negative study cannot completely exclude this[114]
   E. the yield of angiography in ICH would be expected to be lower in patients at increased risk of ICH: patients on warfarin, chronic alcoholics, patients with amyloid angiopathy…

A. a study of 8 ICHs showed autoregulation was maintained, but with an elevated lower limit. However, CBF fell when MAP was lowered pharmacologically below the <u>usual</u> MAP, which averaged 80% of the admission MAP (admission HTN followed the ICH)[110]

NovoSeven® (recombinant activated coagulation factor VII (rFVIIa))

At the site of a tissue factor **(TF)** bearing cell, rFVIIa forms a complex with

TF resulting in thrombin production. It also converts factor X to its active form, Xa on the surface of activated platelets resulting in a “thrombin burst” at the site of damage[116]. Half life: 2.6 hrs. Expensive (≈ $10,000 per dose).

FDA approved for various bleeding diatheses (including hemophiliacs with antibodies to factor VIII or IX). Phase II “off label” Factor Seven for Acute Hemorrhagic Stroke **(FAST)** study for ICH[111] appeared promising, however, preliminary results of the phase 3 trial showed no difference in death or major disability at 90 days.

Rx for ICH. Doses studied: 40, 80 & 160 mcg/kg IV over 1-2 minutes given IV within **4 hours** of symptom onset reduces 90 day morbidity & mortality, with a dose-related reduction in mean increase of ICH volume at 24 hrs, and a small increase in thrombotic complications[A]. **Side effects:** thrombotic events (MI, CVA…) primarily with higher doses (≥ 120 μg/kg)[117], risk may be increased in presence of DIC, predisposing coagulopathy, advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with activated or nonactivated prothrombin complex concentrates (aPCC/PCCs) due to increased levels of circulating TF.

A. studied in patients with GCS > 5, with no plan for surgical evacuation within 24 hours and no history of thrombotic or vaso-occlusive disease

Anticoagulation following ICH

Patients with ICH who require anticoagulation pose a management dilemma. In the case of embolic disease, the fear of extending an ICH or of converting it to a hematoma has traditionally outweighed the possible benefit of protection from further embolization. However, an anecdotal (retrospective uncontrolled) report of 12 such patients found no incidence of increased intracranial bleeding with either continued anticoagulation (6 patients) or resumption of anticoagulation after an hiatus (several days in 4 patients, 5 days in 1, and 14 days in 1)[118]. In another study[119] none of 35 patients who had resumption of warfarin had recurrent intracranial hemorrhage (ICH, SAH or subdural hematoma). While this does not prove that anticoagulation is safe after ICH, it does demonstrate that if there is a strong indication for anticoagulation, and if there is not an acceptable alternative (e.g. Greenfield filter for DVT), that anticoagulation in this setting is not always met with disastrous results.

The probability of having an ischemic stroke at 30 days following cessation

of warfarin for a median of 10 days are approximately 2.9% for patients who had originally been treated with warfarin for prosthetic heart valves, 2.6% for those treated for atrial fibrillation, and 4.8% for those treated for cardioembolic stroke[119A] (see *Cardiogenic brain embolism*, page 1022 for more details).

Antiplatelet therapy after ICH is not associated with a substantially increased risk of recurrent ICH[122] (prospective cohort study).

Recommendation

A-fib: long-term anticoagulation should be avoided after ICH[123].

Mechanical heart valves: **1-2 weeks** off anticoagulation (to observe ICH, or to evacuate a SDH or clip an aneurysm)[119, 124]. Patients with deep hemispheric ICH at high-risk for thromboembolic stroke may benefit from resumption of long-term anticoagulation)[123].

Patients requiring hemodialysis after ICH: heparin-free dialysis may be used.

SURGICAL TREATMENT

Booking the case - craniotomy for ICH

BOOKING

Also see defaults & disclaimers (*page v*).

1. position: (depends on location of bleed)
2. equipment:
   A. microscope (not used for all cases)
   B. image guided navigation (not typically used)
3. post op: ICU
4. consent (in lay terms for the patient - not all-inclusive):
   A. procedure: surgery through the skull to remove blood clot, stop any bleeding identified, possible placement of external (ventricular) drain
   B. alternatives: nonsurgical management
   C. complications: (usual craniotomy complications - *see page v*) *plus* further bleeding which may cause problems (especially in patients taking blood thinners, antiplatelet drugs including aspirin, or those with coagulation abnormalities or previous bleeds) and may require further surgery, areas of the brain that have already been damaged by the bleeding are not likely to recover, hydrocephalus

INDICATIONS

Amazingly, after repeated attempts to penetrate this dilemma, considerable controversy persists regarding indications for surgery. Surgery may lower morbidity from rebleeding (especially if aneurysm or AVM are identified as the cause of the ICH), edema, or necrosis from mass effect of hematoma (unproven), but rarely causes neurologic improvement. Meta-analyses[125, 126] yield inconclusive or conflicting results.

Randomized prospective studies (RPS) in the current CT/surgical era

One RPS[127] found lower mortality for patients with GCS 7-10 treated surgically[B]. However, survivors in this group were all severely disabled (none were independent).

A. these numbers may be gross underestimates as many patients died within 2 weeks, and follow-up imaging was scant[120]. Another study[121] showed a much higher rate of 20%

B. note: only 20% of these patients were operated on < 8 hrs from the bleed, and the mean time for all patients to operation was 14.5 hours (range: 6-48 hrs), which may be long

Another[113] found no benefit from surgery for putaminal hemorrhages, also with poor outcomes in all patients.

International STICH[128]: enrolled 1,033 patient. Study shortcomings: possible selection bias (the responsible neurosurgeon had to be uncertain of the benefits of medical vs. surgical treatment), “early surgery” had a somewhat long median time to treatment of 30 hours, and 26% of medically treated patients crossed over and had surgery at a mean of 60 hours (late). Given these limitations, the conclusion was that for supratentorial ICH there was no benefit of early surgery (although there may have been some benefit in the subgroup with a hematoma within 1 cm of the cortical surface). This trial may be more accurately considered to be a comparison of early vs. delayed surgery in patients subjectively judged to need surgery by the investigator.

A pilot study to investigate minimally invasive procedures (stereotactic instillation of tPA and then aspiration of the clot) is planned.

Conclusion

The decision to operate therefore must be individualized based on patient's neurologic condition, size and location of hematoma, patient's age, and the patient's and the family's wishes concerning "heroic" measures in the face of catastrophic illness.

Guidelines for considering surgery vs. medical management

(for separate indications for surgery for cerebellar hemorrhage, *see below*)

1. **NON-SURGICAL**: factors that favor medical management
   A. minimally symptomatic lesions: e.g. alert patient with subtle hemiparesis (especially patients with GCS > 10127)
   B. situations with little chance of good outcome
      1. high ICH score (*see page 1126*), which overlaps with the following
      2. massive hemorrhage with significant neuronal destruction (*see below*)
      3. large hemorrhage in dominant hemisphere
      4. poor neurologic condition: e.g. comatose with posturing (i.e. GCS ≤ 5), loss of brain stem function (fixed pupils, posturing…)
      5. ≈ age > 75 yrs: do not do well with surgery for this
   C. severe coagulopathy or other significant underlying medical disorder(s): in the event of herniation, rapid decompression may be considered in spite of the risks
   D. basal ganglion (putaminal) or thalamic hemorrhage: surgery is no better than medical management, and both have little to offer[113, 129] (*see below*)
2. **SURGICAL**: factors that favor rapid surgical removal of the blood clot
   A. lesions with marked mass effect, edema, or midline shift on imaging (removal is considered due to the potential for herniation)
   B. lesions where the symptoms (e.g. hemiparesis/plegia, aphasia, or sometimes just confusion or agitation…) appear to be due to increased ICP or to mass effect from the clot or surrounding edema. Symptoms attributable directly to brain injury from the hemorrhage are unlikely to be reversed by surgical evacuation
   C. **volume**: surgery for moderate volume hematomas (i.e. ≈ 10-30 cc) (see *Eq 32-1*, page 1125) may be more appropriate than with:
      1. ✖ small clot (< 10 cc): mass effect is usually not significant
      2. ✖ large clot

a. > 30 cc: associated with poor outcome (only 1 of 71 patients could function independently at 30 days[130])

b. massive hemorrhage

i. > 60 cc with GCS ≤ 8: 91% 30-day mortality[130]

ii. > 85 cc (the volume of a sphere with a diameter of 5.5 cm): no patient survived, regardless of treatment in one series[131]

D. persistent elevated ICP in spite of therapy (failure of medical management). Evacuating clot definitely lowers ICP, but the effect on outcome is uncertain

E. rapid deterioration (especially with signs of brain stem compression) regardless of location in a patient considered to be salvageable

F. favorable location, for example:

1. lobar (as opposed to deep hemispheric): in spite of optimistic results in a non-randomized study done in 1983 indicating good outcomes in patients with deep hemorrhages treated with early surgery[62], a later randomized study failed to confirm this benefit[113]
2. cerebellar: *see below*
3. external capsule
4. non-dominant hemisphere

G. young patient (especially age ≤ 50 yrs): they tolerate surgery better than elderly patients, and, unlike elderly patients with brain atrophy, they also have less room in the head to accommodate the mass effect of clot + edema

H. early intervention following hemorrhage: surgery after 24 hrs from onset of symptoms or deterioration may be of less benefit[127]

Management of cerebellar hemorrhage: Recommendations[132]:

1. patients with a Glasgow Coma Scale **(GCS)** score ≥ 14 and hematoma < 4 cm diameter: treat conservatively
2. patients with GCS ≤ 13 or with a hematoma ≥ 4 cm: surgical evacuation
3. patients with absent brain stem reflexes and flaccid quadriplegia: intensive therapy is not indicated[A]
4. patients with hydrocephalus: ventricular catheter (if no coagulopathy). Caution: do not overdrain to avoid upward cerebellar herniation (*see page 285*). Most cases with hydrocephalus also require evacuation of the clot

A. some authors contend that the loss of brain stem reflexes from direct compression may not be

irreversible[133], and that cerebellar hemorrhage represents a surgical emergency (and that the above criteria would thus deny potentially helpful surgery to some, *see page 1021* for a discussion of cerebellar infarction and decompression)

Surgical considerations

1. send specimens (hematoma, abnormal looking tangle of blood vessels if present, and possibly biopsy walls of hematoma cavity) to pathology for analysis[134] (to rule-out tumor, AVM, amyloid angiopathy…)
2. surgical options:
   A. "standard approach": craniotomy with evacuation of the clot under direct vision (with or without microscope)
   B. stereotactic aspiration with thrombolytic agents has also been used (see *Stereotactic surgery*, *evacuation of intracerebral hemorrhage* on page 782)
   C. endoscopic surgery[135]

Surgical techniques for cerebellar hemorrhage

1. position: lateral oblique with the involved side up (*see page 154*)
2. if rapidity is crucial, a midline skin incision is preferred because it can be taken down quickly with little fear of encountering a vertebral artery
3. craniectomy is preferred over craniotomy to accommodate post-op swelling
4. a prophylactic Frazier burr hole is recommended to allow rapid treatment if postop hydrocephalus develops (*see page 156* for placement, and *page 158* for use), or, a ventricular catheter may be placed to monitor ICP and allow CSF drainage post-op
5. in cases where there has been rupture into the ventricular system, the surgical microscope should be used to follow the clot to the fourth ventricle which is then cleared of clot

*Ventriculostomy **(IVC)** AKA external ventricular drainage **(EVD)***

May be used in patients with intraventricular extension of blood causing acute obstruction of the third ventricular outlet. In these cases, the IVC is usually placed in the lateral ventricle contralateral to the hemorrhage (to avoid putting the catheter directly in clot, which may obstruct the inlets). The prognosis for patients with a significant volume of intraventricular blood is poor. It may be

difficult to maintain the patency of the catheter due to occlusion by clot, tissue plasminogen activator may help (*see below*).

Tissue plasminogen activator (rt-PA)

Intraventricular rt-PA may help lyse clot and maintain catheter patency or reopen a clotted catheter. No well-designed randomized study has been done; but anecdotal evidence suggests it is relatively safe. ✖ In cases of suspected aneurysm, AVM or other vascular malformation, it cannot be used until the source of bleeding has been corrected[136, 137].

Rx: 2-5 mg of rt-PA[136, 138, 139] in NS is administered through an intraventricular catheter **(IVC)**. The IVC is closed for 2 hours after injection[139]. In the low dose CLEAR-IVH (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage) trial (a phase II trial with 52 patients), 1 mg tPA intrathecally via a ventricular catheter every 8 hours up to a maximum of 4 days, was associated with a 30 d mortality of 15% (compared to an expected 80-85%)[140]. Hemorrhagic complication rate was 6%. A phase III trial is underway to confirm this.

OUTCOME

Thalamic hemorrhages that tend to destroy the internal capsule **(IC)** are more likely to produce hemiplegia than hemorrhages lateral to the IC that compress but do not disrupt the IC.

Mortality: The chief cause of death is cerebral herniation[112], occurring mainly during the first week and mostly in patients with initial Glasgow Coma Scale scores ≤ 7. The in-hospital death rate decreased overall during the 1980s but increased for patients ≥ 65 years of age[141].

Quoted mortality rates vary widely, and depend on size and location of clot, age and medical condition of the patient, and etiology of the hemorrhage. Overall, the 30-day mortality rate is ≈ 44% for ICH[1], which is similar to that for SAH (≈ 46%). Patients with lobar hemorrhages (*see page 1119*) tend to fare better than deep ICH (basal ganglion, thalamus…) with only ≈ 11% mortality in 26 of these patients[12].

32.2. ICH in <u>young adults</u>

In a review of 72 patients age 15-45 yrs suffering nontraumatic ICH[142], a presumed cause was found in 76% (*see Table 32-7*). 3 patients had labor or post-partum hemorrhages (*see page 1121* and also *Pregnancy & intracranial hemorrhage* on page 1086).

AVM: lobar hemorrhages in this age group are highly suggestive of AVM. Of 40 lobar hemorrhages, 37.5% were found to be from AVMs[142].

Herpes simplex encephalitis: may produce hemorrhagic changes on CT, especially in the temporal lobes (see *Herpes simplex encephalitis*, page 358).

Drug abuse: especially with sympathomimetics such as cocaine (*see page 1121*) should also be considered in young adults.

Leukemia: ICH may the initial presentation of leukemia in a young adult (may be due to metastases (chloroma) or to thrombocytopenia).

Table 32-7 Causes of spontaneous ICH in young adults[142]

Etiology	%
ruptured AVM	29.1%
arterial hypertension	15.3%
ruptured saccular aneurysm	9.7%
sympathomimetic drug abuse	6.9%
tumor*	4.2%
acute EtOH intoxication	2.8%
pre-eclampsia/eclampsia	2.8%
superior sagittal sinus thrombosis	1.4%
moyamoya	1.4%
cryoglobulinemia	1.4%
undetermined	23.6%

* hemangioma, ependymoma, metastatic choriocarcinoma… (see *Hemorrhagic brain tumors*, page 1123)

Outcome

Overall in-hospital survival (including those treated medically) was 87.5%.

32.3. Intracerebral hemorrhage in the newborn

Occurs primarily in premature infants. Alternate terms: subependymal hemorrhage **(SEH)**, germinal matrix hemorrhage **(GMH)**, periventricular-intraventricular hemorrhage **(PIVH)**. Intraventricular hemorrhage **(IVH)** arises from extension of SEH through ependymal lining of ventricle and occurs in 80% of cases of SEH[143].

ETIOLOGY

The highly vascular germinal matrix is part of the primordial tissue of the developing brain and is the source of future neurons and glial cells. It is located just beneath the ependymal lining of the lateral ventricles, and undergoes progressive involution until 36 weeks gestational age **(GA)**. Thus, the matrix may persist out of utero in premature infants. A disproportionate amount of the total CBF perfuses the periventricular circulation through these capillaries which are immature and fragile and have impaired autoregulation[144, 145]. The site of hemorrhage is age dependent. Between 24-28 weeks GA they occur over the body of the caudate nucleus and at 29 weeks GA or greater they arise over the head of the caudate nucleus[146].

PATHOGENESIS OF PIVH IN THE PRE-TERM INFANT

The metabolically active GM is susceptible to hypotension and hypoperfusion which can lead to infarction. The GM is a vulnerable watershed zone supplied by Heubner's artery (from the anterior cerebral artery), terminal branches of the lateral striate arteries (off the middle cerebral artery) and the anterior choroidal artery (off the internal carotid or middle cerebral artery).

1. postnatal hypoxia due to respiratory distress syndrome related to hyaline membrane disease, pneumothorax and/or anemia can deprive the metabolically active GM of oxygen. This ischemia to the endothelial cells lining the capillaries makes them vulnerable to infarction and then disruption
2. hypercapnia maximally dilates the thin walled vessels of the GM. If this is followed by sudden increases in perfusion the result can be rupture of the vessels
3. increased venous pressure from any cause (labor and delivery, positive pressure ventilation, stimulation, endotracheal suctioning, myocardial failure from ischemia) can result in increased venous pressure in the GM leading to hemorrhage
4. dehydration followed by rapid resuscitation with hyperosmolar solutions increases the intravascular volume by osmotically encouraging the

movement of fluid from tissues into the intravascular space. With associated increases in systemic blood pressure the GM capillaries are at increased risk of rupture

Risk factors for PIVH

Increased cerebral perfusion pressure **(CPP)** with the associated increased cerebral blood flow **(CBF)** and hypoxia are the common denominators for most risk factors for PIVH. The elevated pressure may cause the hemorrhage by rupturing the fragile vessels of the germinal matrix, possibly already damaged by previous insults of high or fluctuating CBF and hypoxia.

Risk factors for PIVH include[147]:

1. those associated primarily with increased CBF or CPP:
   A. asphyxia: including hypercapnia (*see above*)
   B. rapid volume expansion
   C. seizures
   D. pneumothorax
   E. cyanotic heart disease (including PDA)
   F. infants being mechanically ventilated having RDS and fluctuating CBF velocity documented by Doppler flow meter[148]
   G. anemia
   H. decreased blood glucose
   I. arterial catheterization
   J. blood pressure fluctuations
2. younger GA
3. low birth weight
4. acute amnionitis
5. failure to give antenatal steroids during the 48 hours prior to pre-term delivery[149] (i.e. to women at risk of delivering low birth-weight infants): *see page 1133*
6. APGAR's < 4 at 1 minute and < 8 at 5 minutes
7. acidosis
8. coagulopathies
9. general anesthesia for C-section
10. extracorporeal membrane oxygenation **(ECMO)**: due to heparinization in addition to increased CPP
11. maternal cocaine abuse[150]

12. maternal aspirin use

EPIDEMIOLOGY

INCIDENCE

Depends on the method used for detection (many PIVHs are asymptomatic) and the population being evaluated. 540,000 pre-term infants are born in the United States annually. 85,000 are very pre-term (<32 weeks GA) and 385,000 are late pre-term (34-36 weeks GA). 63,000 very low birth weight (<1500 grams) infants are born each year. Of the preemies weighing < 1500 gm birth weight, 20-25% will suffer from a PIVH[151, 152].

In a 1978 study, PIVH was found by CT in 43% (20/46) of preemies with birth-weight < 1500 gm[153]. Mortality in infants with PIVH was 55%, compared to 23% in those without PIVH[153]. Ultrasound **(U/S)** detected PIVH in 90% of 113 preemies < 34 weeks gestation[154] (49% were grade III or IV, *see Table 32-8* for grading).

TIMING

The timing of PIVH has a bimodal distribution. A substantial number occur within 6 hours of birth with 50% occurring within 12 hours of birth[155, 156]. At postnatal days 3-4, a second peak occurs. Only 5% of bleeds will develop after postnatal day 4. Progression of hemorrhage has been documented in 10-20% of infants[156]. Early onset PIVH is more likely to progress and has a higher mortality[157].

PREVENTION

Numerous studies have been conducted to find a method of directly reducing the incidence of PIVH among premature infants. Many are controversial. Optimal resuscitation and neonatal care, with an emphasis on measures which minimize cerebral blood flow fluctuations are key.

Methods which are not widely used but are of historical interest:

- antenatal phenobarbital: studies failed to confirm the ability to reduce PIVH[158]
- postnatal phenobarbital: meta-analysis of 10 controlled trials by the Cochrane Collaboration concluded that postnatal phenobarbital could not be recommended as prophylaxis to prevent PIVH. Its use was also associated with an increased need for mechanical ventilation[159]

- ethamsylate: a 1994 study found that in a series of 334 infants < 32 weeks GA, the ethamsylate group showed no difference from the control group in incidence of PIVH or death[160]. Conclusion: there is little evidence to support the use of ethamsylate for the prevention of PIVH

Methods which are more widely accepted:

- good prenatal care and avoiding pre-term labor
- antenatal corticosteroids: administration of one course of antenatal corticosteroids to women at risk of having premature birth infants reduces neonatal mortality, respiratory distress syndrome and PIVH[161]. Multiple courses of antenatal corticosteroids did not improve outcomes and were associated with decreased head circumference, weight and length at birth[162]
- indomethacin: results in cerebral vasoconstriction and reduces the responsiveness of CBF to changes in CO_2, lowers CBF and increases arterial oxygenation reducing patent ductus arteriosus **(PDA)**. However, use is possibly associated with increased risk of intestinal perforation
- antenatal vitamin K given IM > 4 hrs prior to delivery decreases PIVH from 33% to 5%
- sluicing umbilical cord blood and delaying umbilical cord clamping by 30-120 seconds in premature babies increased hematocrit and decreased PIVH in 5 of 7 studies[163]
- using surfactant to reduce RDS
- minimizing external stimulation (some centers use fentanyl drips)
- steroids to stabilize the GM vessels

CLINICAL

The most commonly used grading system of Papile et al. based on CT or U/S findings is shown in *Table 32-8*. PIVH may present acutely, subacutely. Most commonly, it is discovered incidentally on surveillance U/S.

There is a direct correlation between younger GA and the severity of PIVH. In infants 24-26 weeks GA, 32% will have a Grade III PIVH and 19% will have a Grade IV PIVH compared with infants 31-32 weeks GA, 11% will have a Grade III PIVH and 5% will have a Grade IV PIVH[164].

Table 32-8 Grading subependymal hemorrhage[153]

Grade	Description
I	subependymal

II	IVH without ventricular dilatation
III	IVH with ventricular dilatation
IV	IVH with parenchymal hemorrhage

Presentation

Asymptomatic PIVH

Most PIVHs will be clinically unsuspected, usually with smaller hemorrhages. Retrospectively, these PIVHs may have been suggested by a fall in Hct or delays in neurologic development. These have a 78% 6-month survival, vs. 20% for PIVH showing signs.

Subacute presentation

Usually smaller or more slowly developing hemorrhages. Clinically may present as irritability, reduced motor activity, or abnormal eye movements.

Acute presentation

- changes in muscle tone or activity: usually decerebrate or decorticate posturing, sometimes flaccid paralysis
- seizures: often subclinical
- tense fontanelle
- hypotension
- respiratory and cardiac irregularities: apnea & bradycardia ("**A's and B's**")
- unreactive pupils and/or loss of extraocular muscle movements
- Hct drop > 10%

Hydrocephalus

20-50% of infants with PIVH will develop either transient or progressive hydrocephalus **(HCP)**. Grades III and IV are more often associated with progressive ventricular dilatation than are lower grades (however, HCP may develop even after low grade PIVH[165]). Younger gestational age infants may be at lower risk.

Post PIVH hydrocephalus usually occurs 1-3 weeks after the hemorrhage. Probably caused by cellular debris and/or the toxic effects of blood breakdown products on the arachnoid granulations (communicating HCP), or by an adhesive

arachnoiditis in the posterior fossa or rarely by compression or blockage of critical pathways, e.g. at the sylvian aqueduct (obstructive HCP). In a case of HCP following intrauterine PIVH, aqueductal gliosis was found at autopsy[166].

Possible presentations

Abnormally increasing OFC (crossing percentile curves faster than body weight), lethargy, apnea and bradycardia, vomiting. There is progressive dilatation of the ventricular system on serial U/S or CT.

PATHOPHYSIOLOGY

Deleterious effects of PIVH on the brain are due to[167]:

- destruction of the germinal matrix and glial precursors
- direct injury to neural tissue from hematoma: once hemorrhage resorbs may leave patient with porencephaly or cystic lesions
- pressure of hematoma on nearby brain tissue reducing CBF even to parts of the same hemisphere distant from the hemorrhage[168]
- diffuse decreased CBF following the hemorrhage[169] due to elevated ICP
- injury from the same hypoxic event that precipitated the PIVH
- decreased CPP leads to periventricular leukomalacia (PVL) and cerebral infarction
- periventricular hemorrhagic infarction
- hydrocephalus (*see above*): numerous deleterious effects on the CNS
- seizures: repeated or prolonged seizures may be deleterious to neuronal function

DIAGNOSIS

Ultrasound (U/S)

Performed through the open fontanelles[154]. Accuracy ≈ 88% (91% sensitivity, 85% specificity)[170]. U/S is invaluable because:

- it demonstrates the size of the ventricles, the location and size of the hematoma, and the thickness of the cortical mantle
- it may be brought to the infant’s bedside (obviating transportation)
- it is non-invasive
- it is not adversely affected by occasional infant movements (eliminating the

need for sedation)
- there is no exposure to ionizing radiation (radiation from diagnostic imaging in children has long-term risks for cancer[171] and damage to the lens)
- it may be followed serially with relative ease

CT scan

Sometimes necessary when U/S is not readily available, or in complicated cases where anatomy is difficult to deduce from U/S images.

TREATMENT

General measures are directed at optimizing CPP without further excessive elevation of CBF by carefully maintaining normal MAP and normalizing pCO_2, and by treating ventriculomegaly as outlined below.

While daily LPs can control the deleterious effects of posthemorrhagic HCP, they do not reduce the frequency of long-term HCP (requiring permanent shunting). Ventricular size must be monitored with serial U/S.

Ventriculomegaly

When detected, need to differentiate the following:

- transient ventriculomegaly: occurs in the first few days after PIVH. This may not cause elevated ICP. As implied, it is self limited
- progressive ventriculomegaly: occurs in 20-50% of cases
- "hydrocephalus ex vacuo": due to loss of brain tissue or maldevelopment. Is not progressive on serial U/S. OFCs may fall below normal due to lack of growing brain as stimulus for head growth

MEDICAL TREATMENT

- not very effective. Treated patients fared worse in several studies
- osmotic agents: isosorbide, glycerol. Effects are short-lived
- ✖ diuretic therapy: has been used, but a large study showed increased nephrocalcinosis and biochemical abnormalities, resulting in a borderline increase in the risk for motor impairment at one year[172]. The results were so compelling, the data-monitoring committee terminated the study prematurely. Furosemide and acetazolamide therapy was deemed neither safe nor effective in treating post-hemorrhagic ventricular dilatation and cannot therefore be recommended[173]

SURGICAL/INTERVENTIONAL TREATMENT

Due to poor operative results, surgical evacuation of an intracerebral hemorrhage in the newborn is not indicated with the possible exception of a posterior fossa hemorrhage causing brain stem compression that does not respond to medical treatment[174]. Supportive measures are usually in order.

Intervention for intraventricular blood

34% of infants < 1500 g require shunt/reservoir drainage after failed medical management. Type III and IV PIVH: > 70% of cases develop progressive ventricular dilatation, and 32-47% of this subset will ultimately require shunting[151].

Indications: Intervention for intraventricular blood is indicated in the setting of progressive ventriculomegaly with the OFC crossing percentile curves and clinical evidence of increased ICP (split sutures, tense fontanelle…).

Serial lumbar punctures: Used at many facilities for hemorrhages with intraventricular extension and communicating hydrocephalus (the usual type of HCP that occurs with PIVH)[175].

This should be undertaken with the knowledge that meta-analysis[176] showed sequential lumbar or ventricular taps of ≈ 10 ml/kg/tap for prophylaxis or treatment of progressive hydrocephalus offers no clear benefit over conservative treatment, and had an infection rate of 5-9%. In rare cases, LPs may succeed in temporizing progressive HCP for a few weeks until the infant is large enough for shunt placement.

Infants < 800 gm may not tolerate LPs because of desaturation when lying on their side, or the LP itself may be difficult. In these patients, consider 1-2 ventricular taps to at least obtain fluid for analysis (in some cases nothing further needs to be done).

Serial ventricular taps: May be a viable short-term option for those infants who cannot tolerate LPs or in whom there is obstruction to CSF flow in the lumbar subarachnoid space (e.g. due to spinal subdural hematoma from previous LP). However it is not desirable for long-term use because of repeated trauma to brain (risk of porencephaly) and risk of intracerebral, intraventricular, or subdural hemorrhage.

If continued taps are likely (i.e. large hemorrhage, or rapid recurrence of intracranial hypertension as determined by palpation of fullness of anterior fontanelle **(AF)** following several taps) the acceptable options include:

- continuing serial LPs (*see below*)
- ventricular taps: not recommended for more than a few treatments as it causes porencephaly
- placement of a ventricular catheter connected to a subgaleal reservoir (either a Rickham reservoir, or a low profile McComb reservoir[177]). These can be inserted safely at the bedside, obviating the need for transport to the O.R.[178]
  - temporary ventricular access: the reservoir can be used for serial percutaneous taps. Usually tapped QD or QOD (*see below*). Use a 27 Ga butterfly needle, clean with at least 3 betadine stick swabs, withdraw ≈ 10 ml and send for culture. Reported infection rate: 8-12%[179]
  - ventricular-**subgaleal shunt**: the side-port of the reservoir is left un-capped. A subgaleal pocket must be created at the time of surgery. Fluid is reabsorbed from this potential space. Use has been reported up to 35 days[180]. Infection rate: ≈ 6%
  - the reservoir may be converted to VP shunt if and when appropriate. Not recommended in infants < 1100 gms due to very high infection rate
- external ventricular drainage **(EVD)**: similar to reservoir, but with possibility of inadvertent dislodgment (13%) and comparable infection rate (6%)
- early VP shunting: high infection rate, peritoneal cavity not suitable in many cases, e.g. due to necrotizing enterocolitis **(NEC)**, paucity of subcutaneous tissue through which to pass shunt tube… Not recommended for infants < 2000 gms

Advantages of temporary ventricular access (TVAD)

1. avoids shunt in unhealthy children at risk of infection, skin breakdown or other operative/anesthetic complications
2. clears protein and cellular debris (more favorable for subsequent shunting)
3. avoids repeated penetration of brain with risk of porencephaly
4. provides port for infusion of medication (e.g. antibiotics) PRN
5. avoids cumbersome, easily dislodged EVD with infection risk 6% on average of 13 days of EVD
6. up to 25% of patients will recover and avoid permanent shunt placement[181, 182]

Disadvantages of TVAD

1. requires services of a neurosurgeon (not always available)
2. increases risk of infection of subsequent permanent shunt from 5% to 13% (183
3. inherent risks of surgery including hemorrhage, infection, ventriculitis, meningitis, CSF leak
4. risks of overdrainage including subdural hematoma, impaired skull growth

Serial taps (via ventricular reservoir or LP)

8-20 cc of fluid are removed initially, and this is repeated daily (or more often if AF become very tense before 24 hours elapse) for several days, and then usually varies from 5-20 cc qod to 15 cc TID depending on response. The frequency and volume of the taps are modified based on:

- fullness of AF: attempt to keep AF from becoming tense
- appearance of ventricles on serial U/S: strive to prevent progressive enlargement, reduction in size can usually be achieved
- follow OFC: should not cross percentile curves (need to differentiate from the so-called "**catch-up phase**" of brain growth which may occur once the infant overcomes their overall medical problems and is able to adequately utilize nutrition[184, 185]; serial U/S will show rapid brain growth without progressive ventriculomegaly in cases of catch-up brain growth)
- CSF protein concentration: controversial. Diminishes with serial taps. Some feel that as long as it is ≥ 100 mg/dl it is unlikely that significant spontaneous resorption will occur and continued serial taps will probably be needed
- NB: removal of this volume of fluid may cause electrolyte disturbances, primarily hyponatremia; follow serum electrolytes on regular basis

Follow with serial U/S on day 3-5, and then weekly for several weeks, and then biweekly. A baseline CT scan is often obtained prior to placement of a permanent shunt.

Insertion of VP shunt or conversion of sub-Q reservoir to VP shunt

Indications and requirements:

1. symptomatic hydrocephalus (see *Hydrocephalus*, page 1134) and/or

progressive ventriculomegaly
2. infant is extubated (and thus off ventilator)
3. infant weighs ≥ 2000 grams (some prefer ≥ 2500 grams)
4. no evidence of NEC (might create problems with peritoneal end of catheter)
5. CSF protein ideally < 100 mg/dl (because of concerns about plugging of the shunt, or causing ileus or malabsorption of the fluid[A], and also to see if patient will start reabsorbing CSF on their own)

A. which was not seen with high protein fluid shunted from the subdural space[186]

Technical recommendations:
1. do not tap reservoir for at least 24 hrs before inserting a new ventricular catheter (allows ventricles to expand to facilitate catheterization)
2. obtain U/S the day prior to conversion
3. use a low or very-low pressure system (if CSF protein is high, consider a valveless system), upgrade later in infancy if necessary
4. avoid placing shunt hardware in areas on which these debilitated infants tend to lay (to prevent skin breakdown with hardware exposure)

OUTCOME

Short-term

Preemies with PIVH have higher mortality than matched preemies without PIVH.

The incidence of mortality and progression of hemorrhage is higher the earlier the hemorrhage occurs. The more severe the hemorrhage, the higher the mortality and the higher the risk of HCP (*see Table 32-9*).

Table 32-9 Short-term outcome of PIVH (≈ 250 cases[143])

Severity of hemorrhage	Deaths (%)	Progressive hydrocephalus (%)
mild	0	0-10
moderate	5-15	15-25
severe	50-65	65-100

Long-term

The effect of low grade PIVH on long-term neurodevelopment has not been studied well. Most investigators feel that higher grades of PIVH are associated with greater degrees of handicaps than matched controls.

In one study of 12 infants with Grade II PIVH treated with serial LPs and in the 7 with progressive ventriculomegaly with VP shunt followed for a mean of 4.5 years found all were ambulatory and 75% had IQ within normal range[187].

A recent study of very low birth weight infants showed that children 18-22 months age with severe PIVH and shunts had significantly lower scores on the Bayley Scales of Infant Development IIR compared with children with no PIVH and children with equal grades of PIVH who did not require a shunt[188].

OTHER CAUSES OF INTRACEREBRAL HEMORRHAGE IN THE NEWBORN

- birth trauma may result in subdural hemorrhage, tentorial hemorrhage, parenchymal hemorrhage and/or subarachnoid blood. This is usually detected by imaging (U/S or CT) when an infant develops seizures, apnea, bradycardia or rarely focal neurological deficits. It rarely requires surgical intervention
- choroid plexus hemorrhage can result in IVH. In some cases HCP can develop and require shunt placement
- hemorrhagic stroke has been identified in 6.2 per 100,000 live births[189]. The usual presentation was with encephalopathy (100%) and seizures (65%). 75% of the strokes were idiopathic. Other identified etiologies were thrombocytopenia and a single case of a cavernous malformation. Risk factors for perinatal hemorrhagic stroke include: male gender, fetal distress, emergent c-section, prematurity and post-maturity
- tumors in the neonate can present with hemorrhage
- vascular malformations of any form can present in the neonate with hemorrhage, although this is uncommon. Vein of Galen malformations are diagnosed in the neonate in about 40% of cases[190]. Most of these infants present with fulminant congestive heart failure and 50% have ventriculomegaly

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32.4. References

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NOTES

33. Occlusive cerebrovascular disease

33.1. Atherosclerotic cerebrovascular disease

33.1.1. Carotid artery

Atherosclerotic plaques begin to form in the carotid artery at 20 yrs of age. In the extracranial cerebral circulation, plaques typically start on the back wall of the common carotid artery **(CCA)**. As they enlarge, they encroach on the lumen of the ICA. Calcified hard plaques may not change with time. The risk of CVA correlates with the degree of stenosis and with certain types of plaque morphology, and is also increased in hypercoagulable states and with increased blood viscosity.

PRESENTATION

Carotid artery lesions are considered symptomatic if there is one or more lateralizing ischemic episodes appropriate to the distribution of the lesion. A lesion is considered to be <u>asymptomatic</u> if the patient only has non-specific visual complaints, dizziness, or syncope not associated with TIA or stroke[1]. The majority (80%) of carotid atherothrombotic strokes occur without warning symptoms[2].

Asymptomatic carotid stenosis: Usually discovered as a carotid bruit. Asymptomatic bruit: prevalence increases with age (2.3% in ages 45-54 yrs, 8.2% at $\geq$ 75)[3]. Accuracy of a bruit in predicting ICA stenosis: 50-83% (depending on cohort, criteria for stenosis…). Sensitivity is as low as 24%[4].

Symptomatic carotid disease: May present as a TIA, RIND or CVA with any of the following findings (for ICA *occlusion* syndromes, *see page 1027*):

- retinal insufficiency or infarction (central retinal artery is a branch of the ophthalmic artery): ipsilateral monocular blindness
  A. may be temporary: **amaurosis fugax**, AKA transient monocular blindness **(TMB)**. Four types:

Type I: embolic. Described "like a black curtain coming down" in one eye. Complete loss of vision, usually lasts 1-2 minutes

Type II: flow related. Retinal hypoperfusion → desaturation of color, usually described as a graying of vision

Type III: vasospastic. May occur with migraines

Type IV: miscellaneous. May occur with anticardiolipin antibodies

B. blindness may be permanent

• middle cerebral artery symptoms:
  A. contralateral motor or sensory TIA (arm and face worse than leg) with hyperreflexia and upgoing toe
  B. language deficits if dominant hemisphere involved

EVALUATION OF THE EXTENT OF CAROTID DISEASE

Symptomatic patients will usually be assessed as part of a stroke/TIA protocol.

Check CBC with platelet count, fibrinogen, PT/PTT (to R/O hypercoagulable state).

Funduscopic exam may show **Hollenhorst plaques** (cholesterol crystal emboli).

Overview

Classification of patients based on the hemodynamics and also the embolic propensity of carotid lesions has thus far been too complex to be utilized in large studies. The tests described below place a great deal of emphasis on the greatest degree of stenosis which is probably an oversimplification. Plaque composition and morphology is probably important.

Plaque morphology

"Vulnerable" plaques are atherosclerotic plaques likely to cause thrombotic complications, or those that tend to progress rapidly. Criteria for vulnerable plaques include: intimal thickening, plaque fissure, lipid/necrotic core with thin fibrous cap, calcification, thrombus, intraplaque hemorrhage, and outward remodeling. Some of these features can be identified with high-resolution MRI[5-8].

ASSESSMENT OPTIONS

For recommendations for which tests to use, *see page 1146*.

Angiography

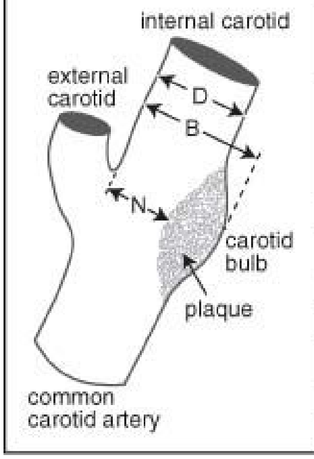
The "gold standard" test is a catheter angiogram. It cannot be justified as a screening test because it is invasive, and too costly and risky (recent data show < 1% risk of transient or permanent deficit[A9-11] in good hands). Also, unlike duplex doppler and MRA, it does not provide any information about the thickness of the plaque. Different definitions of the degree of stenosis are employed, *Table 33-1* compares the definitions used by the NASCET study[12] to that of the ECST[13]. For both, **N** is the linear diameter of the carotid artery at the site of greatest narrowing. The studies differ in the denominator, NASCET uses **D** (the diameter of the normal artery distal to the carotid bulb - taken at the first point at which the arterial walls become parallel), whereas the ECST uses **B** (the estimated carotid bulb diameter).

A. risk is 2-3 times higher in symptomatic patients than asymptomatic

For example, using the NASCET definition, the degree of stenosis is shown in *Eq 33-1*.

$$\begin{matrix}\text{\% stenosis}\\ \text{(NASCET)}\end{matrix} = \left(1 - \frac{N}{D}\right) \times 100 \qquad \textbf{Eq 33-1}$$

Table 33-1 Comparison of NASCET and ECST measurements of ICA stenosis*



NASCET	ECST
$1-\frac{N}{D}$	$1-\frac{N}{B}$
Approximate equivalent degrees of ICA stenosis based on direct comparison† (%)	
30	65
40	70
50	75
60	80
70	85
80	91
90	97

* adapted from Donnan G A, Davis S M, Chambers B R, et al.: Surgery for the Prevention of Stroke. Lancet 351: 1372, 1998, with permission

† shaded boxes indicate degrees of stenosis for which surgery was NOT of clear benefit for *symptomatic* stenosis (*see page 1150*)

The relationship between the degree of narrowing based on the NASCET definition vs. that of the ECST has also been estimated by equation[14] as shown in *Eq 33-2*.

$$\underset{\text{(by ECST)}}{\%\ \text{stenosis}} = 0.6 \times \underset{\text{(by NASCET)}}{\%\ \text{stenosis}} + 40\% \qquad \textbf{Eq 33-2}$$

Angiography also affords the opportunity to perform endovascular intervention if indicated (however, aside from dissections, surgical endarterectomy has been shown to be superior to endovascular techniques).

Duplex doppler ultrasound

B-mode image evaluates the artery in cross-sectional plane, and spectrum analysis shows blood flow. Performs poorly with a “string sign”. Cannot scan above the angle of the mandible. Lower frequencies give greater depth of penetration, but signal definition is sacrificed (used in transcranial doppler). Sensitivity: 88%, specificity: 76%[15].

Magnetic resonance angiography (MRA)

May obviate the need for angiography in some cases of carotid stenosis, specifically in symptomatic patients with a focal “gap” of signal intensity loss with distal reappearance of signal[16, 17]. Sometimes overestimates the degree of stenosis[18]. Sensitivity: 91%, specificity: 88% for extracranial carotid disease[19]. 2D TOF-MRA is adequate (contrast-MRA shows more, but is not necessary for surgical lesions[20]).

Can be performed at the time as MRI with stroke protocol in TIA/stroke patients, and also detects thrombus or dissection. As with Doppler, has difficulties distinguishing very severe stenosis from occlusion. Less operator dependent than Doppler, but is more expensive and time-consuming. MRA is more difficult to perform if the patient is critically ill, unable to lie supine, or has claustrophobia, a pacemaker or ferromagnetic implants. High-resolution MRI may also detect vulnerable plaques (*see page 1145*).

Computed tomography angiography (CTA)

CTA involves ionizing radiation (x-rays) and IV iodinated contrast, limiting its use in patients with dye allergies and renal dysfunction. Results are comparable to MRA and Doppler. CTA can be performed within a few seconds and yields high-resolution images of all vessels from the aortic arch through the intracranial/extracranial vessels as well as the surrounding soft tissues. In a metaanalysis, sensitivity and specificity for detection of a 70% to 99% stenosis were 85% and 93%, respectively[21]. CTA is still evolving and may help detect vulnerable plaques (*see page 1145*). Another potential advantage: ability to obtain CT-perfusion studies at the same time (*see page 128*).

CHOICE OF IMAGING TEST/MANAGEMENT DECISIONS

Despite a great deal of research on the subject, there are no data to support a particular testing algorithm[22]. Doppler, CTA, or MRA are acceptable initial screening tests. In patients with an abnormal screening test, a common strategy is to obtain a second confirmatory noninvasive test to evaluate the carotid bifurcation before intervention. The combination of carotid ultrasound and MRA has proved cost effective with good interobserver reliability[23]. If 2 noninvasive tests are discordant, catheter angiography should be considered before intervention.

TREATMENT

Treatment alternatives are primarily between the following.

1. “best medical management”: *see below*
2. carotid endarterectomy: *see page 1150*
3. endovascular techniques: combined angioplasty and stenting (± distal embolus protection)

MEDICAL TREATMENT

What constitutes “best medical management” has not been precisely determined, and recommendations are constantly changing. Some or all of the following are utilized:

- antiplatelet therapy:
  - usually aspirin **(ASA)** (*see below*)
  - clopidogrel, either alone or in combination with ASA (*see below*)
  - combination of extended release dipyridamole and ASA (Aggrenox®) (no benefit from dipyridamole (Persantine®) alone)
- antihypertensive therapy as appropriate
- good control of diabetes if present
- patients with asymptomatic A-fib should be treated with anticoagulation (see *Cardiogenic brain embolism*, page 1022)
- antilipid therapy if needed
- intervention to help patients to quit smoking

Antiplatelet therapy

aspirin **DRUG INFO**

Irreversibly inhibits cyclooxygenase preventing synthesis of vascular prostacyclin (a vasodilator and platelet inhibitor) and platelet thromboxane A_2 (a vasoconstrictor and platelet activator). Platelets, lacking cellular organelles, cannot resynthesize cyclooxygenase whereas the vascular tissues do so rapidly[24]. NB: < 1000 mg ASA per day probably does not help with high grade stenosis where there is perfusion failure or flow failure. Some (but not all) studies show less effectiveness in women[25], and no large study has shown that ASA prevents a second stroke in patients that have already had one.

Rx: For angina, a bolus dose of 160-325 mg PO is followed by maintenance doses of 80-160 mg/d (lower doses appear to be as effective as higher doses)[26]. Optimal dose for cerebrovascular ischemia continues to be

debated. 325 mg PO qd reduces risk of stroke following TIA by 25-30%. Daily doses of 81 or 325 mg when compared to higher doses were associated with a lower rate of CVA, MI and death (6.2% vs. 8.4%) following carotid endarterectomy[27].

aspirin/ER-dipyridamole (Aggrenox®) **DRUG INFO**

Combination of extended release dipyridamole and ASA (Aggrenox) is more effective than ASA alone for prevention of TIA, stroke, and myocardial infarction[28-30]. Aggrenox was not superior to clopidogrel, with increased hemorrhage with Aggrenox[31]. **SIDE EFFECTS:** H/A with initial therapy.

Rx: 1 capsule PO BID. **SUPPLIED**: fixed dose capsules of aspirin 25 mg/extended-release with dipyridamole 200 mg.

clopidogrel (Plavix®) **DRUG INFO**

A thienopyridine. Incidence of severe neutropenia (0.04%) is close to that of ASA (≈ 0.02%)[32]. Interferes with platelet membrane function by inhibiting ADP-induced platelet fibrinogen binding and release of platelet granule contents, as well as subsequent platelet-platelet interactions. Produces a time and dose dependent irreversible inhibition of platelet aggregation and prolongation of bleeding time. May replace ASA if intolerance or resistance. Used in combination with ASA for some endovascular procedures. Although clopidogrel plus aspirin is recommended over aspirin for acute coronary syndromes, the MATCH[33] results do not suggest a similar benefit for stroke and TIA. Combination therapy significantly increased risk of hemorrhage[33].

PHARMACOKINETICS: Dosed once daily. Requires several days to reach maximal effect (∴ a loading dose may used, e.g. after an acute event such as an MI, or before stenting). Takes ≈ 5 days off the drug for platelet inhibition to reverse.

Rx: 75 mg PO qd. Loading dose: 225 mg (3 pills) the first day of therapy. **SUPPLIED**: 75 mg film-coated tablet.

Choice of antiplatelet agents

Individualization is recommend for antiplatelet agents for secondary stroke

prevention. ASA is effective, and its low cost may help compliance. A small reduction of vascular events with Aggrenox may justify its expense from a broader healthcare perspective. Clopidogrel is appropriate for those intolerant or resistant to ASA. Clopidogrel plus ASA may be indicated in patients with recent cardiac ischemia or vascular stenting[34].

33.1.1.1. Asymptomatic carotid artery stenosis

Key concepts:

- natural history: reveals low stroke rate (2%/yr) half of which are not disabling
- large randomized trials have revealed moderate surgical benefit versus medical management for: asymptomatic stenosis >60%
- treatment selection criteria depend on patient's age, gender and comorbidities (and therefore life expectancy), and on perioperative complication rate

PRACTICE GUIDELINE 33-1 ASYMPTOMATIC CAROTID STENOSIS*

For patients with a surgical risk < 3% and life expectancy ≥ 5 yrs

Level I[36]: carotid endarterectomy **(CEA)** is beneficial for: asymptomatic stenosis ≥ 60%
Level II[36]: unilateral CEA + simultaneous CABG for: stenosis > 60%
Level III[36]: unilateral CEA for: stenosis > 50% with large, deep, complex or cavitated ulcer†

For patients with a surgical risk 3-5%

Level II[36]: ipsilateral CEA for: stenosis > 75% with contralateral ICA stenosis 75-100%
Level III[36]:

- ipsilateral CEA for: stenosis > 75% irrespective of contralateral stenosis
- unilateral CEA + CABG for: bilateral asymptomatic carotid stenosis > 70% + CABG required
- ipsilateral CEA for: unilateral carotid stenosis > 70% + CABG required

For patients with a surgical risk 5-10%

Level III[36]:

- unilateral CEA + CABG for: bilateral asymptomatic stenosis > 70% + CABG required
- ipsilateral CEA + CABG for: unilateral carotid stenosis > 70% + CABG required
- ✖ **Inappropriate indications**[36]:
    - stenosis ≤ 50% irrespective of contralateral carotid artery status
    - ipsilateral CEA for: stenosis > 75% irrespective of contralateral carotid

* NB: slight modifications to this parameter may need to be made in light of further data from ACST[35]. As of this writing, these guidelines have not been updated

† at the time that this guideline was written, more emphasis was placed on these plaque factors

Natural history

Prevalence of carotid stenosis >50% in men and women >65 years of age is 5-10%, with 1% having stenosis >80%[37-39].

Natural history studies reflect an annual stroke risk of 1-3.4% with asymptomatic carotid artery stenosis of 50-99% at 2-3 years[40-45]. A cohort study found similar cumulative rates of ipsilateral stroke over 10 years (9.3%, or 0.9%/year) and 15 years (16.6%, or 1.1%/year)[46].

Attempts to identify subgroups of patients with asymptomatic carotid stenosis at elevated stroke risk suggest that the rate of unheralded stroke ipsilateral to a hemodynamically significant extracranial carotid artery stenosis is 1-2% annually, with some data suggesting that the stroke rate may be higher with progressing stenosis or with more severe stenosis. Asymptomatic carotid stenosis is an important marker of concomitant ischemic cardiac disease[40-42, 45, 46]. In the REACH Study[47], patients with asymptomatic carotid stenosis (n = 3164) had statistically significantly higher age- and sex-adjusted 1-year rates of transient ischemic attack, non-fatal stroke, fatal stroke, and cardiovascular death compared with patients without asymptomatic carotid stenosis (n = 30 329).

Surgery vs. medical management: the studies

ACST[35]

> **Σ** The largest multicenter randomized trial to date[35] revealed a moderate benefit for immediate CEA vs. medical management in patients age < 75 with asymptomatic stenosis ≥ 60%.

Details:[3],120 patients with ≥ 60% stenosis by duplex ultrasound were randomized to immediate CEA (50% had CEA within 1 month, 88% within 1 year) or medical therapy at the discretion of the treating physician. Mean follow-up: 3.4 years. Exclusion criteria included: poor surgical risk, prior ipsilateral CEA, and probable cardiac emboli. Surgeons were required to have a perioperative morbidity and mortality rate of < 6%.

Net five-year risk for all stroke or perioperative stroke or death: 6.4% in the CEA group, vs. 11.8% in the medical group (p<0.0001). Fatal or disabling stroke: 3.5 vs. 6.1%. Fatal stroke alone: 2.1 vs. 4.2%. Although men and women benefited, men benefited more. CEA did not demonstrate a statistically significant benefit for patients over the age of 75. Statistical benefit was not seen in the immediate CEA group until nearly two years after surgery, despite a relatively low perioperative morbidity and mortality rate of 3.1%, (in contrast to patients with *symptomatic* stenosis (NASCET[48]) where benefit was seen much earlier).

ACAS[49]

> **Σ** Large trial that randomized patients in good health with asymptomatic stenosis* ≥ 60% to CEA plus aspirin, or aspirin alone[49] found a reduced 5-year risk of ipsilateral stroke if CEA was performed with <3% perioperative morbidity and mortality and is added to aggressive management of modifiable risk factors.

* calculated in the same manner as the NASCET study

Details: CEA reduced 5-year stroke risk 66% in males, 17% in females (not statistically significant), and 53% overall. CEA did <u>not</u> significantly protect against *major* CVA or death (P = 0.16) (half of the CVAs were not disabling), and was somewhat protective against *any* stroke or death (P = 0.08). Excluded patients (age > 79 yrs, unstable CAD, uncontrolled HTN) may have been higher risk. Surgeons were carefully selected and the surgical morbidity (1.5%) and mortality (0.1%) was very low. Surprisingly, ≈ half of the total morbidity (1.2%) was related to angiography. The implication is that for a generally healthy white male with ACAS > 60%, management with CEA (when performed by a surgeon with a low complication rate, as described) reduces his annual risk of all strokes from 0.5% to 0.17% (the reduction of risk for severe stroke is less). The benefit

from CEA is realized within less than one year after the CEA. This is in contrast to the ACST trial (*see above*) and is most likely due to the lower perioperative event rate. The risk from mortality from other causes (including MI) is ≈ 3.9% per year. Combined CVA and death rates in community hospitals[50] while improved over the last 20 yrs, remains higher at ≈ 6.3% than at centers used in this study.

Veteran's Administration Cooperative Study (VACS)[48]

CEA reduces ipsilateral neurologic events, but did not reduce the rate of ipsilateral CVAs nor death (most deaths were secondary to MI). This trial did not include women and was not powered to detect differences in outcome subgroups.

CASANOVA Study[51]

No difference in outcome between CEA vs. aspirin (new CVA or death), but an un-usual protocol lessened it's statistical validity[52].

Mayo Clinic Asymptomatic Carotid Endarterectomy (MACE) Study[53]

There were no major strokes or deaths in either the medical or the endarterectomy group. Surgically treated patients were not given aspirin, and 26% had an MI compared to 9% in the aspirin-treated medical arm, reflecting the high incidence of concomitant CAD in patients with an asymptomatic carotid artery stenosis.

Current recommendations for CEA in asymptomatic carotid stenosis

The 2006 Primary Prevention of Stroke Guidelines recommend prophylactic carotid endarterectomy for highly selected patients with high-grade asymptomatic carotid stenosis to be performed by surgeons with <3% morbidity/mortality rates (Class I, Level of Evidence A). Patient selection should be guided by an assessment of comorbid conditions and life expectancy, and patient individual factors. For high-risk patients with asymptomatic carotid stenosis, carotid angioplasty/stenting is preferred as a reasonable alternative to CEA (Class IIb, Level of Evidence B). However, due to the reported

periprocedural and overall 1-year event rates, there is uncertainty as to whether this group of patients should have either procedure at all[54].

The guidelines for the European Society of Vascular surgery recommend CEA for asymptomatic men < 75 years old with 70-99% stenosis if the perioperative stroke/death risk is < 3% (Grade A). Given the benefit from CEA in asymptomatic women is significantly less than in men, CEA should be considered only in younger, fit women (Grade A)[55].

Recommendations for screening for carotid stenosis

- the U.S. Preventive Services Task Force (USPSTF) currently recommends against screening for carotid stenosis in the adult general population (grade D recommendation[A])[56]
- the AHA Primary Prevention of Stroke Guidelines does not recommend screening for asymptomatic carotid stenosis[54]
- the American Society of Neuroimaging advised that screening should be considered only for age ≥ 65 years with 3 or more cardiovascular risk factors 57
- the Society for Vascular Surgery recommends ultrasonography screening for age ≥ 55 years with cardiovascular risk factors, such as a HTN, diabetes, smoking, hypercholesterolemia, or known cardiovascular disease 58

A. moderate or high certainty that the service has no net benefit or that the harm outweighs the benefit

33.1.1.2. Carotid endarterectomy

Indications

Table 33-2 shows the status of current studies for the surgical treatment of carotid stenosis (NB: some of the results may be contradictory).

The North American Symptomatic Carotid Endarterectomy Trial[12] **(NASCET)** found that for patients with a hemispheric or retinal TIA or a mild (non-disabling) CVA within 120 days and ipsilateral high-grade stenosis (> 70%), that carotid endarterectomy **(CEA)** reduced the rate of fatal and non-fatal CVAs (by 17% at 18 months) and death from any cause (by 7% at 18 months) when compared to best medical management[A]. Results were twice as good for patients with stenosis from 90-99% than for those with 70-79%. NB: for

differences in techniques for measuring stenosis between NASCET and ECST, see *Table 33-1*, page 1145.

A. when surgery was performed with perioperative risk of stroke or death of 5.8%

For asymptomatic patients, *see page 1147*.

Table 33-2 Summary of study findings for carotid endarterectomy (CEA)*
(modified[59])

Stenosis	Relevant study	Recommendation	Risk reduction†
Symptomatic Narrowing			
70-99%	NASCET[12]	CEA	16.5 @ 2 yrs
> 60%	ECST[13]	CEA	11.6 @ 3 yrs
50-69%	NASCET[60]	CEA‡	10.1 @ 5 yrs
< 30%	NASCET[60]	BMM	0.8 @ 5 yrs
< 40%	ECST[61]	BMM	CEA worse @ 3 yrs
Asymptomatic Narrowing (*see page 1147*)			
> 60%	ACST[35]	CEA if age < 75 yrs	5.4% @ 5 yrs
> 60%	ACAS[49], ACST§	CEA‡	6.3 @ 5 yrs
> 50%	VACS	± CEA Δ	
< 90%	CASANOVA	BMM^Δ	

* abbreviations: NASCET = North American Symptomatic Carotid Endarterectomy Trial; ECST = European Carotid Surgery Trial; CASANOVA = Carotid Artery Stenosis with Asymptomatic Narrowing Operation Versus Aspirin; ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Atherosclerosis Study; VACS = Veteran's Administration Cooperative Study; CEA = carotid endarterectomy; BMM = best medical management

† reduction in risk of all nonfatal CVAs and death from any cause with CEA vs. BMM

‡ surgery moderately beneficial (requires low complication rate)

§ the overall health of the patient is critical

Δ results equivocal, *see text page 1149*

Unresolved controversies

Include:

1. progressive CVA ("stroke in evolution"): see *Emergency carotid endarterectomy*, page 1156
2. abrupt occlusion: see *Emergency carotid endarterectomy*, page 1156

3. tandem lesions (e.g. carotid siphon and bifurcation stenosis): although this topic remains controversial, CEA in patients with tandem lesions has not been associated with increased postoperative stroke rates[62, 63]. Recent case series also report success with endovascular treatment
4. progressive retinal ischemia

Timing with respect to acute CVA

For patients with small fixed deficits or small infarcts on CT or MRI, the risk of early CEA is not increased[62, 64]. In the pooled analysis of the three symptomatic CEA studies, patients randomized in the trials within 2 weeks of the last symptomatic event had greater benefit from CEA[65]. Data from Sundt (see *Pre-op risk factors for CEA* below) indicates that CVA is a risk factor for a complication only if it occurred ≤ 7 days pre-op.

Since the introduction of tPA for the treatment of acute ischemic stroke, there have been reports on the successful treatment of residual critical ICA stenosis following tPA recanalization as early as 24 hours after administration of tPA in patients with small fixed deficit or small ischemic areas on MRI[65, 66].

Pre-op risk factors for CEA

> Σ The characteristics of patients who are high risk for complications from CEA has not been well defined, despite the perception that this group exists.

Identifying patients at high risk for complications after CEA has proven challenging. Typically, the exclusion criteria from studies is cited, but in most cases these are simply patients that were not included in the study because it was the investigators perception these patients might be "high risk". Therefore these risk factors are not validated. They are included here for completeness.

NASCET and ACAS: age> 80 years, prior ipsilateral CEA, prior contralateral CEA within 4 months, prior neck XRT, tandem lesion larger than target lesion, other conditions that could cause symptoms (atrial fibrillation, prior CVA with persistent major deficit, valvular heart disease), major organ failure, uncontrolled hypertension or diabetes mellitus, and significant coronary artery disease[67, 68]).

The SAPPHIRE Trial (Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy): patients with clinically significant cardiac disease (CHF, abnormal stress test, or need for open-heart surgery), severe

pulmonary disease, contralateral carotid occlusion, contralateral laryngeal-nerve palsy, previous radical neck surgery or neck XRT, recurrent stenosis after endarterectomy, and age >80 years[69]. The ARCHeR Trial (ACCULINK for Revascularization of Carotids in High-Risk patients) also included patients with tracheostomy, spinal immobility, and dialysis-dependant renal failure[70].

33.1.1.3. Carotid angioplasty/stenting

> Σ There are no well-designed studies that convincingly show superiority of angioplasty/stenting over CEA in average risk symptomatic patients, and the recommendation in these patients is to continue with the time-tested technique of CEA.

There is a paucity of randomized control trials[69-74] comparing carotid angioplasty/stenting with CEA, and many nonrandomized registries[70, 75-83].

However, data from multicenter randomized trials showing that carotid angioplasty/stenting is as safe over the short term or as efficacious over the long term as CEA in average-risk symptomatic patients are lacking. Published trials are heterogeneous (clinically and methodologically), too small to provide robust and convincing data, and limited in long-term follow-up. Only the SAPPHIRE study[69] comparing CEA with stenting (using a distal embolic protection device) for moderate to severe carotid stenosis with comorbidities that might increase the risk of CEA (high-risk patients), found that angioplasty/stenting was not inferior (risk within 3%, $P = 0.004$) to CEA (based on a composite primary end point of stroke, death, or MI within 30 days, or death from neurologic causes or ipsilateral stroke between 31 days and 1 year)[69]. However, the study methodology has been criticized[84-86].

A 2007 Cochrane review concluded that available data on carotid angioplasty/stenting are difficult to interpret and does not support a change in clinical practice away from recommending CEA as the treatment of choice for suitable carotid artery stenosis[87].

Indications for angioplasty/stenting

Carotid stenting performed with adequate procedural quality levels, should be considered instead of CEA in the presence of[88]:

1. severe vascular and cardiac comorbidities:
   A. congestive heart failure (New York Heart Association class III/IV) and/or known severe left ventricular dysfunction

B. open heart surgery needed within 6 weeks
C. recent myocardial infarction (<24 hours and >4 weeks)
D. unstable angina (Canadian Cardiovascular Society class III/IV)
E. contralateral carotid occlusion

2. specific conditions:
   A. contralateral laryngeal nerve palsy
   B. radiation therapy to the neck
   C. previous CEA with recurrent restenosis
   D. high cervical internal carotid/below the clavicle common carotid lesions
   E. severe tandem lesions
   F. age >80 years
   G. severe pulmonary disease

The 2009 European Society for Vascular Surgery (ESVS) Guidelines state that carotid angioplasty/stenting is indicated in cases of: contralateral laryngeal nerve palsy, previous radical neck dissection or cervical XRT, prior CEA (restenosis), high bifurcation or intracranial extension of a carotid lesion, provided that the peri-interventional stroke or death rate is not higher than that accepted for CEA (Class C recommendation)[55].

AHA Guidelines state that angioplasty/stenting might be a reasonable alternative to CEA in <u>asymptomatic high risk</u> patients. However, they stress that it remains uncertain whether this group of patients should have either procedure[54].

33.1.1.4. Carotid endarterectomy - surgical considerations

PERIOPERATIVE MANAGEMENT

PRE-OP MANAGEMENT (CAROTID ENDARTERECTOMY)

1. ASA 325 mg TID for at least 2 days, preferably 5 days pre-op[89] (NB: patients should be kept on their ASA for surgery, and if not on ASA they should be started, in order to reduce risks of MI and TIA[90])

POST-OP MANAGEMENT (CAROTID ENDARTERECTOMY)

1. patient monitored in ICU with A-line
2. keep patient well hydrated (run IVF ≥ 100 cc/hr for most adults)

3. SBP ideally 110 - 150 mm Hg (higher pressures are permitted in patients with chronic severe HTN)
    A. BP frequently labile in 1st 24 hrs post-op, may be due to “new” pressure in carotid bulb; to prevent rebound hyper- or hypo-tension, avoid long acting agents
    B. hypotension
        1. check EKG - R/O cardiogenic shock
        2. if mild, start with fluids (crystalloid or colloid)
        3. phenylephrine (Neo-Synephrine®) for resistant hypotension
    C. hypertension: nicardipine (Cardene® - *see page 19*) is the agent of choice. Avoid rebound hypotension
4. avoid ASA and dipyridamole for 24-48 hrs post-op (causes oozing); may start these 24-72 hrs post op (note: ASA 325 mg + dipyridamole 75 mg TID have been shown not to reduce the rate of restenosis after endarterectomy[91])
5. optional: reverse half of heparin with protamine 10 minutes after closing arteriotomy

Post-op check (carotid endarterectomy)

In addition to routine, the following should be checked:

- ❑ 1. change in neurologic status due to cerebral dysfunction, including:
    A. pronator drift (R/O new hemiparesis)
    B. signs of dysphasia (especially for left sided surgery)
    C. mimetic muscle symmetry (assesses facial nerve function)
- ❑ 2. pupil diameter and reaction (R/O CVA, Horner’s syndrome)
- ❑ 3. severe H/A (especially unilateral)> may indicate hyperperfusion syndrome
- ❑ 4. STA pulses (R/O external carotid occlusion)
- ❑ 5. tongue deviation (R/O hypoglossal nerve injury)
- ❑ 6. symmetry of lips (R/O weakness of lower lip depressors due to retraction of marginal mandibular branch of facial nerve against mandible, usually resolves in 6-12 wks, must differentiate from central VII palsy due to CVA)
- ❑ 7. check for hoarseness (R/O recurrent laryngeal nerve injury)
- ❑ 8. assess for hematoma in operative site: note any tracheal deviation, dysphagia

POST-OP COMPLICATIONS (CAROTID ENDARTERECTOMY)

To justify CEA, the absolute upper limit of (significant) complication rate should

be ≤ 3%.

1. overall in-hospital mortality: 1%[92]
2. disruption of arteriotomy closure: rare, but emergent (*see below*)
   A. evidenced by:
      1. swelling of neck: rupture may produce a pseudoaneurysm
      2. tracheal deviation (visible, palpable, or on CXR)
      3. symptoms: dysphagia, air hunger or worsening hoarseness, difficulty swallowing
   B. dangers:
      1. asphyxiation: most immediate danger
      2. stroke
      3. exsanguination (unlikely, unless skin closure is also disrupted)
   C. late (often delayed weeks to months): false aneurysm[93]. Risk = 0.33%. Presents as neck mass. Risk is increased with wound infection and possibly with patch graft as compared to endarterectomy alone[93-95]
3. stroke (cerebral infarction) intra-op or post-op rate[96]: 5%
   A. embolic (the most common cause of <u>minor</u> post-op neurologic deficit): source may be denuded media of endarterectomy
   B. intracerebral hemorrhagic **(ICH)** (breakthrough bleeding): occurs in < 0.6%[97]. Related to cerebral hyperperfusion in most[98, 99] (*see below*). Usually occurs within first 2 weeks, often in basal ganglion 3-4 days post-op with hypertensive episode. Patients at greatest risk are those with severe stenosis and limited hemispheric collateral flow
   C. post-op ICA occlusion
      1. most common cause of <u>major</u> post-op CVAs, but may be asymptomatic
      2. risk is reduced by attention to technical details at surgery[100 (p 249)]
      3. some may be due to hypercoagulable state induced by heparin (predictable in patients whose platelet count drops while on heparin. No known therapy for this condition[100 (p 249-50)])
      4. the endarterectomized surface is highly thrombogenic for 4 hrs following endarterectomy (Sundt recommends not reversing heparin)
      5. in Sundt's series using patch graft[100 (p 229)]: 0.8% incidence, associated with major CVA in 33% and minor CVA in 20%
      6. occlusion rate with primary closure: 4% in Sundt's experience, 2-5% in literature[100 (p 249)]

4. post-op TIAs: most due to ICA occlusion. Some may be due to microemboli. Hyperperfusion syndrome produces a 1% incidence of post-op TIAs[100 (p 229)]
5. seizures[101]: usually focal in onset with possible generalization, most occur late (post-op day 5-13) with an incidence of ≈ 0.4%[97] to 1%[102]. May be due to cerebral hyperperfusion[97], emboli[103], and/or intracerebral hemorrhage. Usually difficult to control initially, lorazepam and phenytoin are recommended (*see page 405*)
6. late restenosis: identifiable restenosis occurs in ≈ 25% by 1 yr, and half of these reduce luminal diameters by > 50%[104]. Restenosis within 2 yrs is usually due to fibrous hyperplasia, after 2 yrs it is typically due to atherosclerosis[105]
7. **cerebral hyperperfusion syndrome** (AKA normal pressure hyperperfusion breakthrough): classically thought to result from return of blood flow to an area that has lost autoregulation due to chronic cerebral ischemia typically from high-grade stenosis. Controversial[99]. Usually presents as ipsilateral vascular H/A or eye pain that subsides within several days[106] or with seizures (± PLEDs on EEG, more common with Halothane®, due to petechial hemorrhages[97]). May cause ICH[107]. Most complications occur several days post-op
8. hoarseness: the most common cause is laryngeal edema and <u>not</u> superior nor recurrent laryngeal nerve injury
9. cranial nerve injury: the most common complication after CEA with an incidence of up to 8-10%[108]
   A. hypoglossal nerve → tongue deviation towards the side of injury: incidence ≈ 1% (with mobilizing XII to allow displacement). Unilateral injury may cause speaking, chewing and swallowing difficulties. Bilateral injuries can cause upper airway obstruction[109]. The presence of a unilateral palsy is a contraindication to doing contralateral endarterectomy until the first side recovers. May last as long as four months
   B. vagus or recurrent laryngeal nerve → unilateral vocal cord paralysis: 1% risk
   C. mandibular branch of facial nerve → loss of ipsilateral lip depressor
10. headache[97]
11. hypertension[110, 111]: may develop 5-7 days post-op. Longstanding HTN may occur as a result of the loss of the carotid sinus baroreceptor reflex

COMPLICATION MANAGEMENT

1. post-op TIAs
   A. if TIA occurs in recovery room, emergency CT (to R/O hemorrhage) and then angiogram recommended to assess for ICA or CCA occlusion (vs. emboli)
   B. if TIA occurs later, consider emergent OPG; if abnormal → emergent surgery (if neurologically intact, pre-op angiogram is appropriate)[100]
2. fixed post-op deficit in distribution of endarterectomized carotid
   A. if deficit occurs immediately post-op (i.e. in PACU), recommend immediate re-exploration without delay for CT or angiogram[112] (case reports of no deficit when flow re-established in ≤ 45 mins). For later onset, workup is indicated. Technical considerations for emergency re-operation[100 (p 255)]:
      1. isolate the 3 arteries (CCA, ECA, & ICA)
      2. occlude CCA 1st, then ECA, and ICA last (to minimize emboli)
      3. open arteriotomy, check backflow; if none, pass a No. 4 Fogarty catheter into ICA, gently inflate and withdraw (avoid intimal tears)
      4. if good backflow established, close with patch graft
      5. remove tortuous vessel loops and kinks before closing
   B. immediate management (unless ICH or SDH are likely) includes
      1. fluids (e.g. Plasmanate®) to improve rheology and to elevate BP
      2. pressors (e.g. phenylephrine) to elevate SBP to ≈ 180 mm Hg
      3. oxygen
      4. heparinization (may be controversial)
   C. theoretical benefits of radiographic evaluation include:
      1. CT: identifies ICH or SDH that might require treatment other than re-exploration of the surgical site, elevating BP, etc.
      2. angiogram: identifies whether ICA is occluded, or if deficit is from another cause (e.g. emboli from endarterectomy site) that would not benefit from re-exploration or possibly endovascular treatment
3. disruption of arteriotomy closure, management
   A. **OPEN WOUND** - if there is any stridor, it is critical to do this before trying to intubate (although ideally performed in O.R., the delay may be decisive). Evacuate clot (start with a sterile gloved finger) and stop bleeding, preferably without traumatizing the artery, a DeBakey clamp is optimal
   B. **INTUBATION** - high priority, may be difficult or impossible if

trachea is deviated (open wound immediately). Preferably done by anesthesiologist in controlled setting (i.e. O.R.) unless there is acute airway obstruction

C. call O.R. and have them prepare set-up for endarterectomy, and take patient to O.R.

OPERATIVE TECHNIQUE[100] (191-204)

Anesthesia and monitoring

Most (but not all) surgeons monitor some parameter of neurologic function during carotid endarterectomy, and will alter technique (e.g. insert a vascular shunt) if there is evidence of hemodynamic intolerance of carotid clamping (only occurs in ≈ 1-4%).

1. local/regional anesthesia: permits "clinical" monitoring of patient's neurologic function[113, 114]. Disadvantages: patient movement during procedure (often exacerbated by sedation and alterations in CBF), lack of cerebral protection from anesthetic and adjunctive agents. The only prospective randomized study found no difference between local and general anesthesia[115]. The multicenter, randomized controlled General Anesthesia versus Local Anesthesia (GALA) Trial[116] found no significant differences in the prevention of stroke, MI, or death for either anesthetic technique. Sub-group analysis showed trends (not statistically significant) favoring local anesthesia for perioperative death, event-free survival at 1 year, and patients with contralateral occlusion. Local anesthesia was associated with a significant reduction of shunt insertion[116]. A Cochrane Database Review found no evidence from randomized trials to favor either anesthetic technique[117]
2. general anesthesia, possibly including barbiturates (thiopental boluses of 125-250 mg until 15-30 second burst suppression on EEG, followed by small bolus injections or constant infusion to maintain burst suppression[89])
   A. EEG monitoring
   B. SSEP monitoring
   C. measurement of distal stump pressure after CCA occlusion (unreliable), e.g. using a shunt if stump pressure < 25 mm Hg
   D. transcranial Doppler
   E. near-infrared spectroscopy

Position and incision

1. supine, neck slightly extended and rotated slightly (≈ 30°) away from the operative side
2. the incision curves gently and follows the anterior border of the sternocleidomastoid muscle, and curves posteriorly at the rostral end
3. keep the horizontal portion of the incision ≈ 1 cm away from the mandible to avoid injury to marginal mandibular branch of facial nerve (which lies in the inferior parotid gland and supplies lip depressor) due to retraction against mandible
4. retractors should not be placed deeper than the platysma to avoid injury to recurrent laryngeal nerve which runs between the esophagus and trachea. Blunt retractors are used to avoid internal jugular vein injury

Dissection

1. the common facial vein **(CFV)** usually crosses the field over the carotid bifurcation, it is doubly ligated and divided. It leads to the internal jugular vein **(IJV)**
2. identifying the IJV is key, dissection is carried down between the carotid artery and the IJV
3. the ansa hypoglossi runs superficial to the ICA and serves as a useful guide to the hypoglossal nerve (XII) which should be identified since it is at greater risk when it is not seen. XII can arise anywhere from the carotid bifurcation to the angle of the mandible, although it is usually in the vicinity of the CFV. Mobilization can be facilitated by dividing the small artery (sternocleidomastoid branch of the ECA) and vein that cross over it[109]
4. the ansa hypoglossi can usually be spared, and if mobilized, allows medial retraction of the hypoglossal nerve out of harm's way. If it is necessary to divide the ansa it is done close to the hypoglossal nerve to be certain it is not a branch of the vagus and to minimize neurologic deficit (the ansa has an anterior cervical limb from the cervical plexus)
5. the superior thyroid artery is the first branch of the ECA, and helps differentiate ECA from the ICA (the ICA is located posterior to the ECA)
6. the carotid bulb may be anesthetized with ≈ 2-3 ml of 1% plain lidocaine using a 27 Ga needle. This may be done routinely, or, as some prefer only if hypotension and/or bradycardia occur during dissection (indicating IX nerve stimulation)

7. the ICA must be exposed beyond the extent of the plaque which can be determined by gentle palpation with a moistened finger and by visualization as the area where the artery turns from yellowish to its normal pinker color

Occlusion and arteriotomy

1. a vessel loop is placed around the ECA at least 2 cm above the bifurcation
2. a vessel loop is also placed around the ICA but is looped only once
3. umbilical tape with a choke is placed around the CCA 2-3 cm below the bifurcation
4. heparin (usually 5,000 IU) is given 1 minute prior to cross clamping
5. a temporary aneurysm clip is placed on the superior thyroid artery
6. the order of occlusion of the vessels is as follows (mnemonic: "ICE"):
   - first, the ICA (e.g. with temporary aneurysm clip)
   - second, the CCA (e.g. with a small DeBakey clamp)
   - third, the ECA (e.g. with temporary aneurysm clip)
7. during ICA clamping, mild hypertension is maintained by the anesthesiologist
8. shunt: some surgeons use some form of monitoring (EEG, BSAER, etc.) to determine if a shunt is needed (see *Anesthesia and monitoring*, page 1154), yet others routinely use a shunt whenever possible without assessing the need
9. the arteriotomy is begun in the CCA with a #11 scalpel, and once the lumen is entered, a Potts' scissors carries the incision through to the ICA beyond the plaque. Stay in the midline to facilitate arteriotomy closure

Plaque removal

1. the plaque usually cannot be completely removed form the CCA, and thus it is usually transected with a Potts' scissors taking care not to lacerate the artery wall and to leave as smooth an edge as possible
2. in the ICA, great care must be made to avoid leaving an intimal flap which could become a nidus for an arterial dissection. If necessary the intima may be tacked down by suturing from the lumen out on both ends (using double armed suture) and tying the knot outside the vessel

Arteriotomy closure and vessel release

1. arteriotomy may be performed with a running Prolene suture using either
   A. primary closure
   B. or with a patch graft to increase the caliber of the vessel and reduce the risk of restenosis
   - limited evidence suggests that carotid patch angioplasty may reduce the risk of perioperative arterial occlusion and restenosis. Synthetic patches (Dacron, PTFE) are preferred to autologous vein (risk of aneurysmal dilatation, thrombogenic surface)[55, 118]
2. the order of releasing the vessels: reverse order to clamping
   - first, the ECA
   - second, the CCA (allows air and debris to be washed into the ECA)
   - lastly, the ICA

33.1.1.5. Emergency carotid endarterectomy

Emergency CEA indications include crescendo TIAs and stroke in evolution. The treatment paradigm of these conditions has shifted towards the use of interventional methods, such as thrombolysis and stenting, although there are no randomized controlled trial data to support that approach. A recent meta-analysis of emergent CEA has shown that the pooled stroke and stroke/death rates after CEA for crescendo TIA in 176 patients were 6.5% and 9.0%, respectively. For those with stroke in evolution, the overall stroke and stroke/death rates in 114 patients were 16.9% and 20.0%, respectively[119].

After retrospective analysis of 64 emergency endarterectomies[120] the guidelines given below were suggested. However, the efficacy of immediate surgical removal of obstruction is controversial and unproven. In one early study, over 50% of patients suffered fatal intracranial hemorrhage within 72 hours of emergency carotid endarterectomy.

INITIAL MANAGEMENT OF PATIENT PRESENTING WITH ACUTE NEURO DEFICIT

1. obtain history directed at determining presence of previous CVA and other serious medical illness, and to try to differentiate from seizure
2. baseline neurological assessment including evaluation of STA pulses and carotid bruits
3. during evaluation: close control of BP. O_2 per NC. Labs + EKG (*see Management of TIA or stroke*, page 1016). Consider hemodilution with LMD

4. CT to R/O ICH or infarction (early CVA will not be visible)
5. when carotid disease is suspected, and CT negative for ICH or acute infarct, emergency angiography, MRI/MRA or CTA is performed

Indications for emergency carotid endarterectomy

In patients with acute neurological deficits, the need for rapid decision making often does not allow differentiating between TIA, stroke in evolution and acute stroke, nor in assessing the stability or fluctuating nature of the deficit.

Indications

1. stroke in evolution
2. **crescendo TIAs**: TIAs that abruptly increase in frequency to ≥ several per day
3. following intraarterial thrombolysis, emergent/urgent CEA is indicated for residual critical carotid stenosis[53, 66]

Contraindications

Patients with depressed levels of consciousness or acute fixed deficits.

Surgical management

Again, most cases would now be managed initially with endovascular thrombolysis and stenting. Surgery would considered if this is not an option.

1. for emergency surgery, it is essential that blood pressure be stable
2. in patients with complete occlusion, ICA is not occluded intra-op (to avoid breaking up thrombus, if present)
3. if thrombus present
   - attempt spontaneous extrusion using back pressure
   - if this fails, attempt to remove with smoothened suction catheter
   - if this fails, pass balloon embolectomy catheter as far as base of skull (caution: avoid injury to distal ICA that could cause CCF)
   - obtain intra-op angiogram unless thrombus emerges and backflow is excellent
   - plicate ICA (avoid creating a blind pouch at origin) if there is good back flow or if satisfactory angiography cannot be obtained

Table 33-3 Surgical results

Presenting deficit	Same or improved	Deaths
intact or mild	92%	0
moderate	80%	1 (7%)
severe	77%	3 (13%)

Surgical results

Highest correlation was with presenting neurologic status (*see Table 33-3*).

33.1.1.6. Totally occluded internal carotid artery

10-15% of patients presenting with carotid territory stroke or transient ischemic attacks (TIA) are found to have carotid occlusion. This amounts to an estimated 61,000 first ever strokes and 19,000 TIAs per year in the United States. Prevention of subsequent stroke in symptomatic patients with carotid artery occlusion remains a difficult challenge. The overall rate of subsequent stroke is 7% per year for all stroke and 5.9% per year for ischemic stroke ipsilateral to the occluded carotid artery[121]. These risks persist even despite treatment with antiaggregants and anticoagulants[122]. The prevalence of asymptomatic carotid occlusion is not known, and the incidence of ipsilateral stroke in never-symptomatic carotid stenosis is negligible[123].

Presentation

3 patterns of CVA with acute carotid artery occlusion:

1. stump emboli: produces cortical infarcts. Emboli usually go up the external carotid (higher flow, and reverse flow that may occur through ICA initially prevents emboli from ICA). Later, ICA emboli may occur.
2. whole hemisphere CVA
3. watershed infarct

In symptomatic patients[124]: hemiparetic TIA 53%, dysphasic TIA 34%, fixed neuro deficit 21%, crescendo TIAs 21%, amaurosis fugax 17%, acute hemiplegia 6%. One series had 27% asymptomatic[125]. Patients may have the so-called “slow carotid stroke” of carotid occlusion which is a stuttering progressive stroke.

MRI

With watershed type of CVA: MRI may show so-called “string of pearls” sign (small areas of intraparenchymal increased density on DWI).

NATURAL HISTORY[120]

Patients with mild deficit and angiographically proven ICA occlusion have a stroke rate (in two series) of 3 or 5% per year (2 or 3.3% related to occluded side). In patients with acute ICA occlusion and profound neurological deficit, 2-12% make good recovery, 40-69% will have profound deficit, and 16-55% will have died by the time of follow-up.

ENDOVASCULAR THROMBOLYSIS AND STENTING FOR ACUTE CAROTID OCCLUSION

Case reports and series of endovascular treatment of internal carotid artery occlusion have confirmed the feasibility of this technique. Intraarterial thrombolysis within 6 hours of stroke onset may increase recanalization rates to 37%-100% and clinical improvement to 53%-94% without significant increase in hemorrhagic transformation when compared with intravenous thrombolytic therapy alone[126-131]. Although results appear promising, randomized controlled trials on cervical carotid thrombolysis and/or stenting are lacking.

SURGERY

Options include: endarterectomy, Fogarty balloon catheter embolectomy (utilizing a No. 2 French catheter with 0.2 ml balloon gently passed 10-12 cm up ICA from small arteriotomy made distal to atheromatous plaque[132]), extracranial-intracranial bypass. Restored patency rate is inversely related to suspected duration of occlusion. Chronically occluded ICA has poor patency rate and little gain from reopening.

Determining the exact time of occlusion is frequently impossible. One must often rely on clinical grounds, therefore an occasional chronic occlusion will be included.

Retrograde filling of ICA to petrous or cavernous segment from ECA (e.g. via ophthalmic) or from contralateral ICA is a good sign of operability[124].

Surgical results[124]

32% (15/47 cases) immediate surgical failures (no or minimal back bleeding), at least 3 deaths. Among immediate successes no CVAs and no TIAs. If operated < 2 days reported patency rate 70-100%, from 3-7 days 50-100%, 8-14 days 27-58%, 15-30 days 4-61%, over 1 month (2 series) 20-50%.

Guidelines

Emergency operations for acute neuro deficit associated with total occlusion should not be performed after about 2 hrs. Extremely poor neuro status (lethargy/coma) is a contraindication to surgery. Patients without persistent neuro deficit: operate ASAP. If the patient has recurrent TIAs (despite maximal medical therapy) following recent carotid occlusion, and no definite infarct on MRI, consider bypass surgery.

33.1.2. Vertebrobasilar insufficiency

CLINICAL

DIAGNOSTIC CRITERIA

Table 33-4 shows a mnemonic of the symptoms of vertebrobasilar insufficiency **(VBI)**.

Clinical diagnosis of VBI

Requires 2 or more of the following:

- motor or sensory symptoms or both, occurring bilaterally in the same event
- diplopia: ischemia of upper brainstem (midbrain) near ocular nuclei
- dysarthria: ischemia of lower brainstem
- homonymous hemianopsia: ischemia of occipital cortex (NB: this is binocular, in contrast to amaurosis fugax which is monocular)

Table 33-4 Mnemonic: "The 5 D's of VBI"

• "drop attack"
• diplopia
• dysarthria
• defect (visual)
• dizziness

VBI may be suspected in a patient with transient episodes of "dizziness" (vertigo that is otherwise unexplained, e.g. absence of orthostatic hypotension) that is initiated by positional changes. VBI may sometimes be due to compression of the VA at the C1-C2 level with:

1. head turning (see *Bow hunter's stroke* below)
2. os odontoideum (*see page 966*)

3. anterior atlantoaxial subluxation: e.g. in rheumatoid arthritis (*see page 495*)
4. with rotatory atlantoaxial subluxation: *see page 955*

Symptom complexes

Predicting site of lesion based only on clinical evaluation is very unreliable. Atheromatous and stenotic lesions occur most frequently at VA origin.

VBI symptoms may be due to:

1. hemodynamic insufficiency (may be the most common etiology), including:
   - **subclavian steal**: reversed flow in VA due to proximal stenosis of subclavian artery
   - stenosis of both VAs or of one VA where the other is hypofunctional (e.g. hypoplastic, occluded, or terminates in PICA) causing reduced distal flow in face of inadequate collaterals (see *Bow hunter's stroke* below)
2. embolism from ulcerations
3. atherosclerotic occlusion of brainstem perforators

Natural history

No clinical study accurately defines the natural history. The estimated stroke rate is 22-35% over 5 years, or 4.5-7% per year[133] (one study estimating 35% stroke rate in 5 years did not use angiography).

Risk of CVA after first VBI-TIA has been estimated as 22% for first year[134].

Evaluation

Adequate investigation requires selective four-vessel angiography.

Treatment

Anticoagulation is the mainstay of medical management. Alternatives include anti-platelet drugs such as ASA (efficacy of either remains unproven[133, 135]).

Surgical treatment includes:

- vertebral endarterectomy
- transposition of VA to ICA (with or without carotid endarterectomy, with or without saphenous vein patch graft) or to thyrocervical trunk or to

subclavian artery[136]

- bypass grafting (e.g. occipital artery to PICA)
- C1-2 posterior arthrodesis (*see page 183*) may prevent potentially life-threatening CVA in cases of os odontoideum (*see page 966*)

BOW HUNTER'S STROKE

Bow hunter's stroke **(BHS)**: hemodynamic VBI induced by intermittent VA occlusion resulting from head rotation[137] (ischemic sequelae range from TIA (bow hunter's sign) to completed stroke). May occur with forced (e.g. with chiropractic neck manipulation[138]) or voluntary[139] head rotation.

Occlusion usually involves the VA contralateral to the direction of rotation, and usually occurs at the C1-C2 junction (due to the immobility of the VA at this location)[140]. However, other sites have also been reported[141, 142].

VA occlusion does not produce symptoms in most individuals due to collateral flow through the contralateral VA and/or the circle of Willis. Symptomatic occlusion usually involves the dominant VA[143], however, may also occur with non-dominant VA[139]). Most cases of BHS occur in patients with an **isolated posterior circulation** (incompetent posterior communicating arteries).

BHS has also been postulated as one possible cause of SIDS[144].

Contributing factors:

1. external VA compression[142]
   A. spondylotic bone spurs: particularly in the foramen transversarium[145]
   B. tumors
   C. fibrous bands (e.g. proximal to entrance of VA into C6 foramen transversarium[141])
   D. infectious processes
   E. trauma
2. tethering of the VA
   A. at the transverse foramina of C1 & C2
   B. along the sulcus arteriosus proximal to where the VA enters the dura
3. defect in odontoid process[146]
4. atherosclerotic vascular disease

Diagnosis

BHS should be suspected in patient with symptoms of VBI precipitated by head movement. This may be very difficult to differentiate from vertigo and nausea due to vestibular dysfunction (rotation of the body keeping the head motionless might be helpful[147]).

Dynamic cerebral angiography (DCA): ✖ NB: significant consequences can be precipitated during DCA in patients with BHS[140]. The involved VA shows loss of flow as the head is rotated from the neutral position to the contralateral side. Carotid injections demonstrate patency of P-comms and the presence of any persistent fetal anastomoses.

CT angiogram (CTA): Same precautions as with DCA (*see above*). Probably not the initial diagnostic study of choice. If the DCA is negative, CTA is not needed. If DCA is positive, CTA may be helpful to demonstrate the arterial relationship to the bony anatomy.

Treatment

Options include:

1. anticoagulation[147]
2. cervical collar: to remind patient not to turn their head
3. for VA compression at C1-2 (*see Table 33-5* for a comparison):
   A. C1-2 fusion: *see page 183*
   B. VA decompression: C1 "hemilaminectomy" via a posterior approach[149]
4. for compression at other sites: elimination of the source of compression where possible (e.g. sectioning of offending fibrous band[141], removal of osteophytic spurs[145]…)

Table 33-5 Comparison of surgical treatment for positional VA occlusion at C1-2

Procedure	Advantages	Disadvantages
C1-2 fusion	high success rate in eliminating symptoms	loss of 50-70% of neck rotation with possible discomfort
VA decompression	no loss of motion	33% continue to have symptoms[148]

Management recommendations: For compression at C1-2, it is suggested that VA decompression be performed as the initial treatment. This should be followed by DCA to verify maintenance of patency with head turning. Patients who fail

clinically or on DCA should undergo C1-2 fusion[140]. Patients need to know pros and cons of each option.

VERTEBROBASILAR HYPOPLASIA

Reported as a possible etiology for cerebellar CVA.

33.2. Cerebral arterial dissections

Key concepts:

- hemorrhage into the medial layer of an artery
- may be spontaneous or post-traumatic, may be intracranial or extracranial
- may present with pain (usually ipsilateral H/A or carotidynia), Horner's syndrome (in carotid dissections), TIA/CVA, or SAH
- extracranial dissections are usually treated medically (anticoagulation), intracranial dissections with SAH are treated surgically

This section primarily discusses "spontaneous" dissections. ICA dissection following blunt cervical trauma is much more common, and is covered on *page 984*.

NOMENCLATURE

Some confusion has arisen because of inconsistent terminology in the literature. Although by no means standard, Yamaura[150] has suggested the following:

dissection	extravasation of blood between the intima and media, creating luminal narrowing or occlusion
dissecting aneurysm	dissection of blood between the media and adventitia, or at the media, causing aneurysmal dilatation, which may rupture into the subarachnoid space
pseudoaneurysm	rupture of artery with subsequent encapsulation of the extravascular hematoma, may or may not produce luminal narrowing

PATHOPHYSIOLOGY

The lesion common to all dissections is hemorrhage outside of the vascular lumen due to pathological trans-intimal extravasation of blood from the true

lumen into the vessel wall. The hematoma may either dissect the internal elastic membrane from the intima[151] causing narrowing of the true lumen, or it may dissect into the subadventitial plane producing an adventitial outpouching from the vessel wall (pseudoaneurysm). Rupture through the vessel wall producing SAH occurs occasionally.

Subintimal dissection is more common with intracranial dissections, whereas extracranial vessels (including the aorta) usually dissect at the media or between media and adventitia.

"Spontaneous" dissections have been associated with a large number of conditions, oftentimes the association is unproven. These conditions include:

- fibromuscular dysplasia **(FMD)**: found in ≈ 15% of cases[152]
- cystic medial necrosis (or degeneration): originally thought to be a common finding, now thought to perhaps be linked to a higher likelihood of fatal dissection
- saccular aneurysm
- Marfan syndrome: autosomal dominant inherited disorder of connective tissue. Phenotypic manifestations are due to production of abnormal fibrillin
- atherosclerosis: only rarely implicated as an etiology. More likely to be a factor with subintimal dissection of *extra* cranial arteries
- Takayasu's disease
- medial degeneration
- syphilitic arteritis (more common in the past, associated with 60% of dissections before 1950)
- autosomal dominant polycystic kidney disease: associated with a higher incidence of cerebral aneurysms (*see page 1057*)
- variant periarteritis nodosa
- allergic arteritis
- homocystinuria
- moyamoya disease[153] (*see page 1170*)
- strenuous physical activity

Epidemiology

Occurs primarily in middle aged patients, with a mean age of ≈ 45 yrs (average age of traumatic dissections is slightly younger). More frequent in men[150, 152]. Incidence is unknown, since often times the condition produces

mild, transient symptoms. Increased awareness of the condition has resulted in an increased rate of diagnosis. ICA dissection accounted for 2.5% of first strokes in one series[154].

The largest reported series[150] (literature review + new cases) of 260 cases found the incidence by location shown in *Table 33-6*. The vertebral artery was the most common intracranial site. Previously, the ICA has been cited as the most common site. This change may be due to the recent increased recognition of arterial dissections as a source of SAH (and vertebral dissections most often present as SAH). Multiple dissections occur in ≈ 10% (the most common: bilateral vertebrobasilar lesions).

Table 33-6 Spontaneous intracranial dissections by site

Location	Left	Right	Total
vertebral	122	82	204
basilar	35		35
internal carotid	17	13	30
middle cerebral	16	10	26
anterior cerebral	10	3	13
posterior cerebral	7	9	16
PICA	4	10	14
Total	176	127	338

Clinical

Cerebral arterial dissections may cause symptoms by:

- embolization secondary to:
  - platelet aggregation stimulated by the exposed surfaces
  - dislodged thrombus (formation of which is enhanced by reduced flow)
- reduced distal flow secondary to:
  - thrombosis due to reduced flow
  - occlusion of the true lumen by the expansion of the mural hematoma
- subarachnoid hemorrhage (atypical presentation, may be more common with posterior circulation dissection than with anterior circulation)[155]

The most common presentation in patients < 30 yrs of age was due to internal carotid dissection without SAH. In patients > 30 yrs, vertebrobasilar artery **(VBA)** dissection with SAH was the most common[150].

Headache, usually severe, often predates neurologic deficit by days or weeks. See following sections (ICA *page 1162*, and vertebrobasilar *page 1163*)

for specifics.

EVALUATION

CT

More useful for evaluating brain for infarction. Dissection can sometimes be visualized directly[156].

CT angiogram (CTA)

Often obviates the need for cerebral angiography since CTA scanners with ≥ 16 detectors are equal in predictive value and have an accuracy near 99%[157].

Angiography

The definitive diagnostic study. However, diagnosis may be delayed if the dissection is misinterpreted as:

1. an unusual saccular aneurysm (the most common error)
2. atherosclerotic lesions: with dissections, the location is unusual, the lesion may be isolated, the age is usually younger, and the stenosis is smooth
3. vasospasm following SAH: however, the narrowing with vasospasm is delayed in onset vs. the changes with dissection which are present from the beginning

Angiographic findings may include:

1. luminal stenosis: irregular stenosis over long segments of the artery often with focal areas of near total stenosis ("**string sign**")
2. fusiform dilation with proximal or distal narrowing (string and pearl sign)
3. occlusion: artery usually tapers to a point
4. intimal flap: when seen, usually found at proximal end of dissection
5. may see proximal beading ("string of beads" configuration, indicative of FMD)
6. "**double lumen sign**": true vessel lumen and a intramural false lumen with an intimal flap. Usually with retention of contrast within the false lumen well into the venous phase. The only pathognomonic sign
7. wavy "ripple" appearance
8. severe kinking (frequently bilateral). With VBA lesions: dolichoectasia

A characteristic of arterial dissections is that they often change configuration on repeat angiography[158] (some resolve, and some worsen).

MRI

Probably not as accurate as CTA or angiography. Optimal MRI study is source T1WI axial images with fat suppression ("fat sat"), look for loss of visualization over several slices, with good visualization above and below. May visualize intimal flap and distinguish a dissection from a fusiform aneurysm.

Crescent sign: bright signal in wall of ICA on T2WI axial images (hematoma in vessel wall).

OUTCOME

An early review of the literature found an 83% mortality within a few weeks of presentation with vertebrobasilar artery **(VBA)** dissection[159]. A later report tempered that grim prognosis[160].

Based on a review of 260 cases[150], an overall mortality of 26% was found. 70% had a favorable outcome (based on Glasgow Outcome scale), 5% poor. Mortality was higher in ICA lesions (49%) than VBA lesions (22%). Mortality was 24% in the SAH group, and 29% in non-SAH cases.

33.2.1. Internal carotid dissection

See *Cerebral arterial dissections* above for general information.

SPONTANEOUS

Some cases considered spontaneous may actually be due to trivial trauma, including violent coughing, nose blowing, and simple neck turning. Usually seen in young women.

In spontaneous dissection, the most common initial symptom is ipsilateral headache. Most of these (60%) are orbital or periorbital, but they may also be auricular or mastoid (39%), frontal (36%), temporal (27%). May also produce sudden onset of severe pain over carotid artery (**carotidynia**)[95].

Incomplete Horner's syndrome (**oculosympathetic palsy**): ptosis and miosis without anhidrosis (due to involvement of plexus around the ICA, sparing the ECA plexus which innervates facial sweat glands) may occur. Bruits may be heard by the examiner or by the patient. These and other clinical features are shown in *Table 33-7*.

May be a cause of infantile and childhood hemiplegia and hemiparesis[161].

Table 33-7 Clinical features of spontaneous ICA dissection[152]

Feature	%
focal cerebral ischemia	76%
headache	59%
oculosympathetic palsy	30%
bruit	25%
amaurosis fugax	10%
neck pain	9%
syncope	4%
scalp tenderness	2%
neck swelling	2%

POSTTRAUMATIC (NONPENETRATING)

Posttraumatic ICA dissection is much more common than spontaneous, and is covered on *page 984*.

33.2.2. Vertebrobasilar system artery dissection

VERTEBRAL ARTERY DISSECTIONS

See *Cerebral arterial dissections* on page 1160 for general information. Less common than carotid dissection (16th case of extracranial dissection in literature reported in 1987162). Extracranial lesions outnumber intracranial.

Traumatic dissections tend to occur where the VA crosses bony prominences, e.g. at the C1-2 junction or where it enters the foramen transversarium (usually at C6). Spontaneous dissections tend to be intracranial and commonly occur on the dominant VA.

SPONTANEOUS

Has been associated with FMD, migraine, and oral contraceptives[162]. Unrecognized or forgotten trauma or sudden head motion may have occurred in some cases reported as spontaneous. Commonly occurs in young adults (mean age: 48 yrs). With spontaneous dissections, 36% of patients have dissections at

other sites, 21% of cases have bilateral VA dissections[163].

Dissecting aneurysms of the VA (possibly a distinct entity) are also described[164-166]. They tend to be fusiform, and may be amenable to clipping, and were associated with vertebral dissections in 5 of 7 cases reported in one series[167]. As of 1984, only ≈ 50 cases of dissecting aneurysms were published[167].

POST-TRAUMATIC (NONPENETRATING)

See *page 985*.

PRESENTATION

In spontaneous extradural dissections, neck pain is a prominent early finding in most patients, and is commonly located over the occiput and posterior cervical region. Generalized severe headache is also common. TIAs or stroke (usually lateral medullary syndrome[168] (*see page 1028*) or cerebellar infarction, especially in patients with occlusion of the third or fourth portion of the VA[169]). None of 5 patients developed new neurologic symptoms after the original stroke in an average of 21 months follow-up[169]. In 3 of these 5, VA dissection was bilateral.

Dissecting aneurysms may present with altered consciousness, and may cause SAH (seen in 6 of 30 cases of vertebrobasilar complex dissections)[167]. Rebleeding occurs in 24-30% of those cases presenting with SAH[163], making these lesions treacherous, with a very high mortality[170, 171].

Traumatic extradural dissections or pseudoaneurysms may have a similar presentation, but can also produce massive external hemorrhage or neck hematomas[163].

EVALUATION

See section under *Cerebral arterial dissections*. on page 1162.

Angiography

Diagnosis by angiography may be difficult in many cases (the most common misdiagnosis is ruptured saccular aneurysm of unusual shape[172]).

In post-traumatic dissections, the most common finding is irregular stenosis of horizontal loops of distal extracranial VAs as they pass behind C1, often bilateral.

In 14 of 15 post-traumatic VA dissections, the lesion was located posterior to the atlas (distal extracranial 3rd segment), the single exception being a patient with direct trauma causing proximal VA involvement. This predilection is possibly explained by the fact that the first and third portions of the VA are movable, whereas the second and fourth are relatively immobilized by bone.

TREATMENT

Except for cases presenting with hemorrhage or large ischemic stroke, medical therapy should be started emergently, and consists of anticoagulation, with heparin acutely, followed by oral agents (e.g. Coumadin) probably for a total of 6 months.

As with traumatic dissections, endovascular techniques are now assuming more prominent role in management.

Indications for intervention

Surgery or endovascular techniques (mostly stents, but also occlusion, angioplasty[163]) are required for dissections presenting with SAH (due to their propensity to rebleed) and is recommended for most intradural dissections. For extradural lesions it is indicated for dissections that progress (angiographically) or for persistent symptoms in spite of adequate medical therapy. Some less malignant lesions may be amenable to endovascular stenting.

Surgical treatment

At the time of surgery, the site of dissection may be recognized by fusiform or tubular enlargement of the artery with discoloration due to blood within the arterial wall (the discoloration has been described as black, bluish, purple, purple red, or brown[172]).

Surgical treatment of intradural dissection when endovascular techniques are not an option includes the following alternatives:

1. non-clippable aneurysms may be candidates for Hunterian occlusion of the VA proximal to the BA (either by microsurgical technique, or by endovascular techniques which may not be as precise). Some may not tolerate clipping the dominant VA, especially if the contralateral VA is hypoplastic. Conversely, some may tolerate bilateral VA occlusion[173]). Balloon test occlusion[163] is recommended
    A. if the dissection involves the PICA origin, then clip proximal to

dissection. PICA then fills from retrograde flow, and the reversal of flow across the site of dissection should push the intima back against the wall

   B. if the dissection is proximal to PICA and doesn't involve PICA, then trap the aneurysm between clips. PICA fills by retrograde flow
   C. if the aneurysm begins distal to the PICA origin, occlude the VA[155] distal to the PICA takeoff[174]
2. combining VA clipping (*see above*) with vascular bypass, options:
   A. side-to-side PICA-PICA anastomosis
   B. transplantation of the PICA origin to the VA outside the aneurysm
   C. occipital artery-to-PICA bypass
3. resection accompanied by autogenous interposition vein graft
4. non occlusive surgical techniques
   A. clipping with specially designed clips for fusiform aneurysms (e.g. SundtKees clip)
   B. wrapping: of dubious benefit

VERTEBROBASILAR SYSTEM DISSECTIONS EXCLUDING THE VA

Basilar artery dissections tend to present with brain stem infarction and more rarely with SAH[171]. The prognosis is generally regarded as poor. Endovascular techniques may be able to treat some.

33.3. Extracranial-intracranial (EC/IC) bypass

Includes but not limited to superficial temporal artery-middle cerebral artery **(STAMCA)** bypass.

EC/IC BYPASS FOR ATHEROSCLEROTIC OCCLUSIVE DISEASE

The EC/IC bypass study: The EC/IC bypass, pioneered by Donaghy and Yasargil in 1967175, plummeted in popularity[176] after publication of the international cooperative EC/IC bypass study[177] in 1985. The EC/IC trial randomized 1377 patients with symptomatic ICA or MCA stenosis to either STA-MCA bypass or medical therapy with ASA. Despite a graft patency rate of 96%, surgical patients suffered more and earlier fatal and nonfatal strokes.

Patients with severe MCA stenosis and those with persistent symptoms following ICA occlusion fared especially worse with bypass. During the 55.8 months mean follow-up, the percentage of patients experiencing 1 or more strokes in the medical group compared to the surgical group was 29% vs. 31%.

Critics highlight the failure of the study's inclusion criteria to distinguish between hemodynamic vs. thromboembolic causes of stroke[122, 178, 179] (ischemia secondary to thromboembolic events would not be expected to improve with flow augmentation, and inclusion of such patients in the surgical arm could therefore artificially lower the apparent efficacy of the procedure).

Current state of affairs: Imaging technologies introduced since the EC/IC trial can identify flow-dependent ischemia. Xenon-CT, TCD, SPECT, and MRI may be used in combination with acetazolamide challenge to evaluate cerebrovascular reserve and reactivity (*see page 1011*).

As cerebral perfusion pressure decreases in severe atherosclerotic occlusive disease, cerebral autoregulation is unable to maintain adequate CBF to meet metabolic demands. In this state of "**misery perfusion**," oxygen extraction fraction **(OEF)** of available blood flow will increase[180, 181]. Abnormal OEF, as quantified by PET, is an independent predicator of subsequent stroke[122]. Patients with abnormal response to acetazolamide challenge (*see page 128*) and/or with elevated OEF are therefore potential candidates for cerebral revascularization[122, 179, 182-184].

Other indications for EC/IC bypass

1. aneurysms: certain aneurysms are not amendable to either direct microsurgical clipping or endovascular coiling due to extreme size, location, calcification or atherosclerosis, dissection, or the incorporation of perforators or major arteries. EC/IC bypass remains a highly viable adjunctive measure in patients requiring Hunterian occlusion of parent vessel or prolonged temporary occlusion for definite treatment[185-189]. Cerebrovascular reserve and need for bypass can be assessed preoperatively using balloon test occlusion (BTO) with hypotensive challenge
2. tumors encasing or invading major arteries
3. moyamoya disease: *see page 1170*

Bypass types

The type of graft used depends on preoperative determination of amount of

flow augmentation necessary, the size of the recipient graft and the availability of donor vessel[190]:

1. pedicled arterial grafts: STA, occipital artery
   A. low-flow (15 - 25 ml/min)
   B. only one anastomosis required
   C. 95% graft patency in STA-MCA bypasses
2. radial artery graft
   A. moderate to high flow (40 - 70 ml/min)
   B. advantages: physiological conduit for arterial blood; constant location makes it easy to harvest; lumen size closely approximates that of M2 or P1 and reduces flow mismatch with subsequent flow turbulence and graft thrombosis
   C. disadvantages: risk of vasospasm (reduced with pressure distension technique)
   D. > 90% graft patency at 5 years
3. saphenous vein graft
   A. high flow (70 - 140 ml/min)
   B. advantages: easy accessibility; longer length
   C. disadvantages: risk of thrombosis at distal anastomosis due to flow mismatch and turbulence; lower graft patency rates
   D. 82% graft patency at 5 years

33.4. Cerebrovascular venous thrombosis

3 types of cerebrovascular venous thrombosis **(CVVT)** (may produce venous infarctions):

1. dural sinus thrombosis **(DST)**
2. cortical venous thrombosis
3. deep venous thrombosis

ETIOLOGIES

Many conditions have been incriminated with CVVT. Some common ones are listed below (see reference[191 (p 1301)] for extensive list):

1. infection
   A. usually local, e.g. otitis media[192, 193] (leading to the now obsolete term

otitic hydrocephalus), sinusitis, peritonsillar abscess, paranasal sinusitis[194]

   B. meningitis

2. pregnancy & puerperium: *see below*
3. birth control pills **(BCP)** (oral contraceptives)[195]
4. dehydration and cachexia (marantic thrombosis): includes burns and cachexia of neoplastic disease
5. cardiac disease (including CHF)
6. ulcerative colitis **(UC)**: 1% of UC patients have some thrombotic complication (not necessarily intracranial), and this is the cause of ≈ 33% of deaths (usually pulmonary embolism)
7. periarteritis nodosa
8. sickle cell trait
9. trauma: including closed head injury (*see below*)
10. iatrogenic: e.g. S/P radical neck surgery[196], transvenous pacemaker placement, post-craniotomy
11. malignancy: including myeloproliferative disorders
12. hypercoagulable state (AKA thrombophilia)
    A. protein C deficiency or resistance to activated protein C
    B. antithrombin III deficiency
    C. protein S deficiency
    D. antiphospholipid antibodies: associated with a variety of clinical syndromes including ischemic CVA, DVTs, thrombocytopenia, systemic lupus erythematosus (*see page 1025*)
    E. paroxysmal nocturnal hemoglobinuria **(PNH)**
    F. plasminogen deficiency
    G. systemic lupus erythematosus[197]
    H. factor VIII elevation[198]: may explain some cases of CVVT in pregnancy (*see below*)
13. diabetes mellitus: especially with ketoacidosis
14. homocystinuria: *see page 1024*
15. Behçet's syndrome[199]: *see page 78*
16. rarely associated with lumbar puncture[200]

★ In the absence of factors such as BCP use, CVVT is highly suggestive of myeloproliferative disorder.

Pregnancy/puerperium

Highest risk is in first 2 wks post-partum. One series[201] found no case of CVVT occurred later than 16 days post-partum. Incidence ≈ 1/10,000 births. Etiology may be related to elevation of clotting factors (VII, X and especially factor VIII[202]).

Trauma

A rare sequelae of closed head injury[203]. CVVT occurs in ≈ 10% of combat injuries involving the brain. May occur in absence of skull fracture. CVVT should be suspected in patients with fractures or missiles crossing sinus.

FREQUENCY OF INVOLVEMENT OF DURAL SINUSES AND OTHER VEINS

1. sinuses
   A. superior sagittal sinus **(SSS)** and left transverse sinus **(TS)** (70% each)
   B. multiple sinuses in 71%
   C. inferior sagittal sinus: rare, first case report in 1997204
   D. straight sinus[205]
2. superficial cortical veins
3. deep venous system (e.g. internal cerebral vein)
4. cavernous sinus[206, 207]: rare. Thrombophlebitis of the cavernous sinus may be caused by sphenoid sinusitis

PATHOPHYSIOLOGY

Venous thrombosis reduces venous outflow from the brain and diminishes effective blood flow to the involved area. This venous engorgement causes white matter edema. The increased venous pressure may also lead to infarction and/or hemorrhage. These processes may all elevate ICP. Thus, clinical findings may be due to elevated ICP, and focal findings may be due to edema and/or hemorrhage. Cerebral infarction in this setting is called venous infarction.

CLINICAL

Clinical presentations of DST are shown in *Table 33-8*. There are no pathognomonic findings. Many signs and symptoms are due to elevated ICP. May present as a syndrome clinically indistinguishable from idiopathic intracranial hypertension (pseudotumor cerebri) (*see page 713*).

There is a high association of concurrent thromboembolic disease in other

organs.

The anterior 1/3 of the SSS may occlude often without sequelae. Posterior to this, venous infarction is more likely to develop. Midportion SSS occlusion usually → increased muscle tone ranging from spastic hemi- or quadriparesis to decerebration. Posterior SSS thrombosis → field cuts or cortical blindness, or massive CVA with cerebral edema and death. Occlusion of the TS may occur without deficit unless the contralateral TS is hypoplastic, in which cases presentation is similar to posterior SSS occlusion.

SSS occlusion alone will not cause cranial nerve findings except perhaps for visual obscuration and abducens (VI) nerve palsy from elevated of ICP. Thrombosis in the jugular bulb may compress the nerves in the jugular foramen pars nervosa causing hoarseness, aphonia, difficulty swallowing and breathlessness (see *Vernet's syndrome*, page 115)[209].

Table 33-8 Presentation of dural sinus thrombosiss

Sign/symptom	Series A*	Series B*
H/A	100%	74%
N/V	75%	–
seizures	70%	29%
hemiparesis	70%	34%
papilledema	70%	45%
blurred vision	60%	–
altered consciousness	35%	26%

* series A: 20 young females[201]; series B: 38 cases from France[208]

DIAGNOSIS OF DST

Angiography is better at demonstrating where there is residual flow, and can identify areas of reversal of flow. Sometimes angiography will demonstrate clot. CT & MRI are better for identifying areas of clot. Angiography is often used as a complementary test[210].

CT SCAN

Non-contrast CT

May be normal in 10-20% of cases of DST. Findings include:

1. hyperdense sinuses and veins (high density clots in cortical veins produce the **cord sign** which is pathognomonic for cerebral venous thrombosis; seen in only 2/30 patients)
2. petechial "flame" hemorrhages (intraparenchymal): seen in 20% (suspect sinus thrombosis with intracerebral hemorrhages in unusual locations for aneurysm or "hypertensive" hemorrhage)
3. small ventricles: seen in 50%
4. thrombosis of superior sagittal sinus may produce a triangular-shaped high density within the sinus (some refer to this as the **delta sign**, but this causes confusion with the "empty delta sign", *see below*) (there is also confusion when an apparent "empty delta sign" is seen without contrast, this may occur when there is blood surrounding the SSS, e.g. following subarachnoid hemorrhage, this has been called a "false delta sign" or **pseudodelta sign**[211]). Recommendation: avoid the confusion of the "delta signs" and describe the findings
5. white matter edema
6. above changes occurring bilaterally

IV contrast CT

Findings of DST include:

1. with contrast, the dura around the sinus may enhance and become denser than clot in 35% of cases[212]. Near the Torcular herophili this produces what has been called the **empty delta sign**[213], but sometimes this, too, is called the **delta sign**
2. gyral enhancement occurs in 32%
3. dense deep (white matter) veins (collateral flow)
4. intense tentorial enhancement (common)

MRI

Excels for diagnosis and follow-up. Shows absence of flow and clot burden, also demonstrates parenchymal changes. Can differentiate occluded sinus from congenital absence. Shows cerebral edema and non-acute hemorrhagic changes to better advantage than CT. Also may help estimate age of clots (*see Table 33-9*). MR-angiography may increase the utility. MR-venography (MRV) tends to overestimate the degree of occlusion.

Table 33-9 MRI appearance of thrombosed sinuses at various stages

Age of clot in sinus	— Appearance of clotted sinus —	
	T1WI	T2WI
acute	iso-intense	decreased (black): can mimic flow void
subacute	increased (1st)	increased (2nd)
late (> 10 d, recanalized)	black (flow void)	black (flow void)

Angiography for DST

Accuracy close to MRI. MRI has some advantages over angiography (e.g. on angiography a hypoplastic transverse sinus may not visualize, or non-opacified blood entering a sinus may mimic a filling defect).

Findings include:

1. non-filling of segments of sinuses, or filling defects
2. prolonged circulation time: in 50% of cases (may need delayed films to see veins)
3. stumps and abnormal collateral pathways

LP

OP usually increased. CSF bloody or xanthochromic.

Bloodwork

To detect predisposing conditions when the etiology is unknown. Some tests that may be useful include evaluation for thrombophilia (protein C and S levels, antiphospholipid antibodies) as well as tests for specific predisposing conditions (CBC, Factor II level, serum homocysteine level, paroxysmal nocturnal hemoglobinuria (PNH) panel, leukocyte alkaline phosphatase).

Ultrasound for DST

May be used in diagnosis of superior sagittal sinus thrombosis in the neonate[214].

Evaluation for underlying disorder

At the time of presentation, work-up is difficult because the acute process will cause numerous abnormalities in clotting system. The best time to work these patients up is ≈ 3 months after they recover from the acute phase.

Treatment

Should be aggressive because recoverability of brain is probably greater than with arterial occlusive stroke. Management is complicated because measures that counteract thrombosis (e.g. anticoagulation) tend to increase the risk of hemorrhagic infarct (the risk of which is already increased), and measures that lower ICP tend to increase blood viscosity → increased coagulability.

Specific measures

1. correct underlying abnormality when possible (e.g. antibiotics for infection)
2. **heparin** (systemic): (*see* *page 39* for dosing) especially if patient is in DIC. Several studies show a lower mortality rate with heparin than without[215-217]. It remains the best treatment even when there is evidence of intracerebral hemorrhage with the attendant risk of increasing the size of the hemorrhage[210]. There is no consensus on duration of treatment or if warfarin should be used afterwards. Success rate may be higher if administered before patient becomes moribund
3. avoid steroids (reduces fibrinolysis, increases coagulation)
4. control HTN
5. anticonvulsants to control seizures
6. monitor ICP if patient continues to deteriorate: ventriculostomy preferred, but caution must be used if patient is on heparin
   A. hydrate aggressively as ICP tolerates
   B. measures to lower ICP: in general, order is almost reverse of that for traumatic intracranial hypertension because diuretics → hypertonicity → ↑ viscosity → ↑ coagulation
      a. elevate HOB
      b. hyperventilation
      c. drain CSF
      d. pentobarbital coma
      e. use hyperosmotic and/or loop diuretics last. Replace fluid loss with isotonic IV fluids to prevent dehydration (i.e. goal is hypertonic euvolemia)
7. thrombolytic therapy: either systemically or infused directly into clotted sinus[210, 218], may be followed with heparin
   A. urokinase[205, 218] or streptokinase
   B. intravenous **tissue plasminogen activator (tPA)**: promising animal evidence[219], not yet reported in humans

8. when above measures fail, either
   A. decompressive craniectomy (± decompressive lobectomy): this decreases ICP, but may not improve outcome

   OR

   B. direct "attack" on clotted sinus: direct surgical treatment when deficit progresses in spite of above measures, or ICP not manageable (i.e. failure of medical therapy) (*see below*)
9. interventional neuroradiology: effectiveness is much reduced with chronic clot
   A. Penumbra® system: sucks out clot, only takes out a small amount of clot
   B. MERCI® retriever: corkscrew shaped wire that pulls clot out (*see page 1018*)
   C. AngioJet®: not FDA approved for this. Not used for *arterial* clots because of injury to cerebral tissue, but may have some efficacy with venous clot
10. visual loss with papilledema may be treated with optic nerve sheath fenestration/decompression[220]
11. long-term treatment after resolution of acute phase with heparin and/or warfarin **x** 3-6 months

DIRECT SURGICAL TREATMENT FOR DST

Rarely indicated. Thrombectomy and sinus reconstruction are technically possible, but rethrombosis is common. Surgery may be indicated for abscess requiring excision.

Surgical technique for direct treatment of SSS thrombosis

Have available: blood for massive transfusion, large bore IV access, sinus shunt (pre-fabricated, or improvise with high-vacuum silicone grease inside & outside pediatric anode endotracheal tube with cuff on both ends, gas sterilize, prepared pre-op), tissue for sinus reconstruction (e.g. 20 cm of saphenous vein (arteries have a high rate of fibrosis, and there is no published experience with synthetics grafts). Vein grafts are dilated with heparinized saline and should be oriented correctly in case of valves).

Expose a wide portion of the sinus.

Consider ligation when lesion in non-critical location (SSS anterior to

rolandic vein, non-dominant transverse or sigmoid, minor sinuses on skull base).

Hemorrhage is controlled by digital pressure, Fogarty catheter (insert directly, or insert a no. 7 Fogarty thru tiny sinotomy proximal to bleeding which allows repair of bleeding site), and/or insertion of shunt.

PROGNOSIS

Mortality: approximately 30% (range: 5-70%) (10% in French series[208]).

Poor prognosticators:

1. clinical status:
   - A. coma[221]:
   - B. rapid neurologic deterioration[221], focal signs.
2. demographics
   - A. age: extremes of age (infancy or elderly)[221] and age > 37 years
   - B. male gender
3. radiographic findings:
   - A. hemorrhages, especially larger hemorrhages
   - B. venous infarcts
4. deep venous involvement

33.5. Moyamoya disease

Key concepts:

> • progressive bilateral spontaneous occlusion of ICAs with compensatory capillary collaterals that look like a "puff of smoke" (Japanese: moyamoya) on angio
> • typical presentation: juvenile form → ischemic infarcts/TIAs (suspect diagnosis in any child presenting with TIAs). Adult form → hemorrhage
> • pathology: intimal thickening w/o inflammation, may also involve heart. kidneys
> • evaluation: cerebral angiography is necessary to delineate degree of stenosis as well as to evaluate potential extracranial donor vessels for revascularization
> • treatment:
> ◆ medical treatment (antiplatelet drugs, anticoagulation, vasodilators…): not

shown to be effective although antiplatelet/anticoagulation is often used
- surgical revascularization: reduces the incidence of CVAs and TIAs, but benefit on reducing the rate of hemorrhage is unproven

Progressive spontaneous occlusion of one or usually both ICAs (usually at the level of the siphon) and their major branches, with secondary formation of anastomotic collateral capillary network at the base of the brain which has been termed "moyamoya", the Japanese word for something hazy like a "puff of cigarette smoke"[222] (which it fancifully resembles on angiography). With progression, involvement includes the proximal MCAs and ACAs and on rare occasion the vertebrobasilar system. Associated aneurysms (*see below*) and rarely AVMs[223, 224] may be observed.

Eventually the dilated capillary (moyamoya) vessels disappear with the development of collaterals from the ECA (meningeal collaterals are called "**rete mirabile**").

Pathophysiology

Most common pathology is stenosis of the proximal anterior and middle cerebral arteries that is non-atherosclerotic or inflammatory in origin. Exact etiology is unknown but some studies show elevated basic fibroblast growth factor in the dura and scalp arteries in patients with moyamoya[225]. The internal elastic lamina of affected vessels may be thinned or duplicated. Similar vascular changes may also occur in the heart, kidney and other organs, suggesting it may be a systemic vascular disease.

Associated aneurysms

Intracranial aneurysms are frequently associated with moyamoya disease **(MMD)**. This may be a result of the increased flow through dilated collaterals, or it may be that patients with moyamoya may also have a congenital defect in the arterial wall that pre-disposes them to aneurysms. 3 types: 1) usual sites of aneurysms in the Circle of Willis, 2) in peripheral portions of cerebral arteries, e.g. posterior/anterior choroidal, Heubner's, and 3) within moyamoya vessels. The frequency of aneurysms in the vertebrobasilar system is ≈ 62% which is much higher than in the general population[226]. Aneurysmal SAH may be the actual cause of some hemorrhages that were erroneously attributed to moyamoya vessels.

EPIDEMIOLOGY

Risk factors: A history of inflammation in the head & neck region has been implicated.

Demographics: Incidence in Japan is higher (0.35/100,000/yr) than in North America. Two peaks (may not be same disease): juvenile (highest peak), age < 10 yrs (mean 3); adult, 3rd & 4th decade. Slight female predominance (1.8:1). Some evidence for familial tendency (some Asian families have an incidence as high as 7%), genetics appears autosomal dominant with low penetrance. Associated with some HLA antigens (B40 in juvenile form; B54(20) in adult).

Secondary moyamoya disease: AKA "quasi-moyamoya disease" or "moyamoya syndrome"[227]. Agiographic findings of moyamoya associated with e.g.:

- Graves' disease/thyrotoxicosis
- history of cerebral inflammatory disease, including meningitis (especially tuber-cular (TB) meningitis and leptospirosis)
- retinitis pigmentosa
- vascular disorders: atherosclerosis, fibromuscular dysplasia, pseudoxanthoma elasticum
- congenital disorders: Down syndrome, Marfan syndrome, Turner syndrome, neurofibromatosis type 1, tuberous sclerosis, Apert syndrome
- hematologic disorders: Fanconi anemia, sickle cell anemia (in the U.S. one of the more common associations) and sickle cell trait
- following radiation therapy for skull base glioma in children[228]
- head trauma
- systemic lupus erythematosus (SLE)

Natural history

Incidence of disease progression in one study was 20% in adult patients with MMD[229]. Female patients had a higher risk of disease progression than males.

Prognosis of untreated MMD is poor, with 73% rate of major deficit or death within 2 years of diagnosis in children, and similarly poor outlook in adults[230].

PRESENTATION

Juvenile form: Moyamoya is associated with 6% of childhood strokes[225]. Ischemic presentation more common (81%); includes TIAs (41%) which may

alternate sides (alternating hemiplegia is a suggestive clinical finding), RINDs, or infarct (40%). Neurologic events are often provoked by straining or by hyperventilation (e.g. during crying or blowing a wind instrument) which is thought to produce hypocapnea with reactive vasoconstriction.

Headache is the most common presenting symptom, but seizures, focal neurologic deficits, choreoathetotic movements and hemorrhages can also be presenting symptoms. The risk of hemorrhage is increased in stages 5 & 6 of MMD ().

Adult form: Hemorrhage has been described as being more common (60%). Rupture of the fragile moyamoya vessels produces bleeding in the basal ganglia **(BG)**, thalamus or ventricles (from the ventricular wall) in 70-80% of hemorrhages. SAH may occur, usually due to rupture of associated aneurysms (*see above*). In the pre-CT era, the most common form of hemorrhage was thought to be SAH from the rupture of moyamoya vessels, but most cases were probably intraventricular blood or SAH from associated aneurysms[231].

EVALUATION AND DIAGNOSIS

CT

Work-up in suspected cases typically begins with a non-enhanced head CT. Up to 40% of ischemic cases have normal CT. Low density areas **(LDAs)** may be seen, usually confined to cortical and subcortical areas (unlike atherosclerotic disease or acute infantile hemiplegia which tend to have LDAs in basal ganglia as well). LDAs tend to be multiple and bilateral, especially in the PCA distribution (poor collaterals), and are more common in children.

MRI AND MRA

MRA usually discloses the stenosis or occlusion of the ICA. Moyamoya vessels appear as flow voids on MRI (especially in basal ganglia) and a fine network of vessels on MRA, and are demonstrated better in children than adults. Parenchymal ischemic changes are commonly shown, usually in watershed areas.

ANGIOGRAPHY

In addition to helping to establish the diagnosis, angiography also identifies suitable vessels for revascularization procedures. The angiography-related complication rate is higher than with atherosclerotic occlusive disease. Avoid

dehydration prior to and hypotension during the procedure. Six angiographic stages of MMD are described in *Table 33-10*[222] that tend to progress up until adolescence and stabilize by age 20.

Diagnosis of moyamoya requires bilateral[A] symmetrical stenosis or occlusion of the terminal portion of the ICAs as well as the presence of dilated collateral vessels at the base of the brain[225]. Other characteristic findings include:

- stenosis/occlusion starting at termination of ICA and at origins of ACA and MCA
- abnormal vascular network in region of BG (intraparenchymal anastomosis)
- transdural anastomosis (**rete mirabile**), AKA "vault moyamoya". Contributing arteries: anterior facial, middle meningeal, ethmoidal, occipital, tentorial, STA
- moyamoya collaterals may also form from internal maxillary artery via ethmoid sinus to forebrain in frontobasal region

A. if unilateral, the diagnosis is considered questionable[232], and these cases may progress to bilateral involvement

Table 33-10 Six angiographic stages of MMD[222]

Stage	Finding
1	stenosis of suprasellar ICA, usually bilateral
2	development of moyamoya vessels at base of brain; ACA MCA & PCA dilated
3	increasing ICA stenosis & prominence of moyamoya vessels (most cases diagnosed at this stage); maximal basal moyamoya
4	entire circle of Willis and PCAs occluded, extracranial collaterals start to appear, moyamoya vessels begin to diminish
5	further progression of stage 4
6	complete absence of moyamoya vessels and major cerebral arteries

EEG

Non-specific in the adult. Juvenile cases: high-voltage slow waves may be seen at rest, predominantly in the occipital and frontal lobes. Hyperventilation produces a normal buildup of monophasic slow waves (delta-bursts) that return to normal 20-60 seconds after hyperventilation. In > 50% of cases, after or

sometimes continuous with buildup is a second phase of slow waves (this characteristic finding is called "**rebuild-up**") which are more irregular and slower than the earlier waves, and usually normalize in ≤ 10 minutes[233].

Cerebral blood flow (CBF) studies

CBF is decreased in children with MMD, but relatively normal in adults. There is a shift of CBF from the frontal to the occipital lobes[234] probably reflecting the increasing dependency of CBF on the posterior circulation. Children with MMD have impaired autoregulation of CBF to blood pressure and CO_2 (with more impairment of vasodilatation in response to hypercapnia or hypotension than vasoconstriction in response to hypocapnia or hypertension)[235].

Xenon (Xe-133) CT can identify areas of low perfusion. Repeating the study after an acetazolamide challenge (which causes vasodilatation) evaluates reserve capacity of CBF and can identify areas of "steal" which are at high risk of future infarction.

TREATMENT

No medical or surgical treatment has been proven effective in reducing the rate of hemorrhage in the adult with MMD. However, multiple large case series have supported the efficacy of cerebral revascularization for reducing the incidence of ischemic strokes and TIAs[227].

Medical treatment

Medical treatment with platelet inhibitors, anticoagulants, calcium channel blockers[230], steroids, mannitol, low-molecular-weight dextran and antibiotics have not proven to be of benefit. Steroids may be considered for involuntary movements and acutely during recurrent TIAs.

Surgical treatment

Patients with mass effect from clot may be candidates for urgent decompression. Revascularization procedures, however, should be performed when the patient is stable under nonemergent conditions.

Suggested criteria for revascularization procedures[227]:

1. patients presenting with infarction or hemorrhage but are in good neurologic condition

2. infarction < 2 cm maximal diameter on CT, and all previous hemorrhages have completely resolved
3. angiographic stage is II-IV (*see Table 33-10*)
4. timing of operation: ≥ 2 months after most recent attack

Surgical revascular options: Various methods to revascularize the ischemic brain, include:

1. direct revascularization procedures: results are superior to indirect revascularization procedures[236, 237] if a donor and recipient vessel of sufficient caliber (≥ 1 mm outer dia) can be identified (may be difficult in the pediatric age group who are the most likely to benefit[238]). Otherwise, indirect revascularization procedures (*see below*) are options
• STA-MCA bypass[239]: the procedure of choice
2. indirect revascularization procedures: usually reserved for younger patients (suggested cutoff age ≈ 15 years). May be combined with STA-MCA bypass. Includes:
   A. encephalomyosynangiosis **(EMS)**: laying the temporalis muscle on the surface of the brain (may cause problems with muscle contractions during talking and chewing, and neural impulses on surface of brain)
   B. encephaloduroarteriosynangiosis **(EDAS)**[240, 241]: suturing the STA with a galeal cuff to a linear defect created in the dura. Variations on this technique include splitting the dura[242]
   C. omental transposition[243]: either as a pedicle graft or as a vascularized free flap. Felt to have higher potential to revascularize ischemic tissue than above procedures, but there is greater risk of mass effect from the thickness of the omentum
3. the above indirect revascularization procedures improve blood flow in the MCA distribution, but not ACA circulation. This may be rectified by:
   A. simple placement of frontal burr holes with opening of the underlying dura and arachnoid[244]
   B. "ribbon EDAS" where a pedicle of galea is inserted into the interhemispheric fissure on both sides[245]
4. stellate ganglionectomy and perivascular sympathectomy: unproven that this increases CBF permanently

Postoperatively following STA-MAC bypass procedures:

1. avoid hypertension: may cause bleeding at anastomotic site and in areas of increased perfusion within the brain

2. avoid hypotension: may result in graft occlusion
3. aspirin is started on the post-op day #1
4. watch for evidence of CSF leak
5. monitor coag studies and correct abnormalities
6. cerebral arteriogram is recommended 2-6 months post-op

ASYMPTOMATIC MOYAMOYA DISEASE

Guidelines for management of asymptomatic moyamoya disease have not yet been established. Multi-center, nation-wide survey in Japan focusing on asymptomatic moyamoya disease provided the following findings[246]: subtle findings of cerebral infarction and disturbed cerebral hemodynamics were detected in 20% and 40% of the involved hemispheres, respectively. Angiographic stage was more advanced in elderly patients. Of 34 medically-treated patients, 7 experienced TIA, ischemic stroke or hemorrhage during a mean follow-up period of 43.7 moths. Cerebral infarction or hemorrhage did not occur in the 6 patients who underwent surgical revascularization.

PROGNOSIS

Neurologic status at time of treatment generally predicts long-term outcome[225]. The mortality rate in adults (≈ 10%) is higher than for juveniles (≈ 4.3%)[232]. The cause of death was bleeding in 56% of 9 children and 63% of 30 adults. With treatment the prognosis is good in 58%[231].

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NOTES

34. Outcome assessment

Cancer

Karnofsky performance scale (KPS): *Table 34-1*, often used for grading functional status in patients with cancer. A KPS score < 70 (particularly with brain tumors) often identifies patients with a worse prognosis for any given treatment.

Table 34-1 Karnofsky performance status scale (modified[1, 2])

Score	Criteria	General category
100	normal: no complaints, no evidence of disease	Able to carry on normal activity and work. No special care is needed
90	able to carry on normal activity: minor signs or symptoms	
80	normal activity with effort: some signs or symptoms	
70	cares for self: unable to carry on normal activity or to do active work	Unable to work. Able to live at home, care for most personal needs. Variable assistance is required
60	requires occasional assistance: cares for most of needs	
50	requires considerable assistance and frequent care	
40	disabled: requires special care and assistance	Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be rapidly progressing
30	severely disabled: hospitalized; death not imminent	
20	very sick: hospitalized; active supportive care needed	
10	moribund: fatal processes are progressing rapidly	
0	dead	

Head injury

The **Ranchos Los Amigos scale** (*Table 34-2*) is often used in rating

disability following head injury. The **Glasgow outcome scale** (*Table 34-3*) is frequently employed in outcome assessment.

Table 34-2 Ranchos Los Amigos cognitive scale

Level	Meaning
I	No response to pain, touch, sight or sound.
II	Generalized reflex responses to pain.
III	Localized response. Blinks to strong light, turns towards/away from sound, responds to physical discomfort, inconsistent responses to commands.
IV	**Confused - Agitated** Alert, very active, agitated, aggressive, or bizarre behaviors. Performs motor activities but behavior is non-purposeful, extremely short attention span.
V	**Confused - Non agitated** Gross attention to environment, easily distracted, requires continual redirection, difficulty learning new tasks, agitated by excess stimulation. May converse socially but with inappropriate verbalizations.
VI	**Confused - Appropriate** Inconsistent orientation to time and place. Retention span and recent memory impaired. Begins to recall past, consistently follows simple commands, goal directed behavior with assistance.
VII	**Automatic - Appropriate** Performs daily routine in highly familiar environment in a non-confused but automatic "robot-like" fashion. Skills deteriorate in unfamiliar environment. Lacks realistic planning for future.
VIII	**Purposeful - Appropriate**

Table 34-3 Glasgow outcome scale[3]

Score	Meaning
5	good recovery – resumption of normal life despite minor deficits ("return to work" not reliable)
4	moderate disability (disabled but independent) – travel by public transportation, can work in sheltered setting (exceeds mere ability to perform "activities of daily living")
3	severe disability (conscious but disabled) – dependent for daily support (may be institutionalized, but this is not a criteria)
2	persistent vegetative state – unresponsive & speechless; after 2-3 weeks, may open eyes & have sleep/wake cycles
1	death – most deaths ascribable to primary head injury occur within 48 hrs

Cerebrovascular events

Several outcome grading scales have come to be favored for use following CVAs or SAH. Each emphasizes different aspects of outcome. The Barthel Index

(*see below*) places weight on activities of daily living **(ADLs)**, while others, such as the **modified Rankin scale**[4] (*Table 34-4*) assess levels of independence and includes a comparison to *previous* activity levels. While it does measure functional status, the modified Rankin is not sensitive to subtle neurologic deficits such as dysphasia or visual field defects.

Table 34-4 The modified* Rankin scale

Grade	Description
0	no symptoms at all
1	no significant disability despite symptoms: able to carry out all usual duties & activities
2	slight disability: unable to carry out all previous activities. Able to look after own affairs without assistance
3	moderate disability: requiring some help, but able to walk without assistance
4	moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	severe disability: bedridden, incontinent, and requiring constant nursing care and attention

* the original Rankin scale 5: did not have Grade 0, Grade 1 did not include the words “despite symptoms” and “& activities”, and it defined Grade 2 as “unable to carry out some of previous activities…”

Table 34-5 The Barthel index

Item	Original Barthel Index			Modified Barthel Index				
	Unable to perform task	Needs assistance	Fully independent	CODE 1 Unable to perform task	CODE 2 Attempts task but unsafe	CODE 3 Moderate help required	CODE 4 Minimal help required	CODE 5 Fully independent
Personal hygiene	0	0	5	0	1	3	4	5
Self bathing	0	0	5	0	1	3	4	5
Feeding	0	5	10	0	2	5	8	10
Toilet	0	5	10	0	2	5	8	10
Stair climbing	0	5	10	0	2	5	8	10
Dressing	0	5	10	0	2	5	8	10
Bowel control	0	5	10	0	2	5	8	10
Bladder control	0	5	10	0	2	5	8	10
Ambulation	0	5-10	15	0	3	8	12	15
Wheelchair*	0	0	5	0	1	3	4	5
Chair/bed transfers	0	5-10	15	0	3	8	12	15
TOTAL (range)	0	→ →	100	0		→ → → → →		100

* score only if unable to walk and patient trained in wheelchair management

Barthel index: The original Barthel index[6, 7] assigns one of three scores to 10 ratable ADLs, and then the individual scores are summed (*see Table 34-5*). The

modified Barthel index **(MBI)** with a 5-step scoring system as shown in *Table 34-5* appears to have greater sensitivity[8]. The total ranges from 0 to 100 (a score of 100 implies functional independence, not necessarily normality).

Of all the factors, independence in bathing was the most difficult. Abilities on the Barthel index tend to return in a fairly consistent order, and so most patients with the same score will have similar patterns of disability.

Spinal cord injury

Functional Independence Measure™[9-11] **(FIM™):** developed to provide uni-form evaluation of disability for spinal cord injuries. Rates 18 items shown in *Table 34-6* (13 motor, 5 cognitive) on the 7 level scale shown in *Table 34-7*.

The FIM™ has high internal consistency and is a good indicator of burden of care[12, 13].

Table 34-6 The Functional Independence Measure™ (FIM)

Classification	Item
Motor	
Self-care	1. Eating
	2. Grooming
	3. Bathing
	4. Dressing - upper body
	5. Dressing - lower body
	6. Toileting
Sphincter control	7. Bladder management
	8. Bowel management
Mobility	9. Bed, chair, wheelchair
	10. Toilet
	11. Tub, shower
Locomotion	12. Walk or wheelchair
	13. Stairs
Cognitive	
Communication	14. Comprehension
	15. Expression
Social cognition	16. Social interaction

	17. Problem solving
	18. Memory

Table 34-7 The 7 FIM™ rating levels of disability

Degree of dependency	Level of function	Score
No helper	Complete independence	7
	Modified independence	6
Modified dependenc on a helper	Supervision	5
	Minimal assist (≥ 75% independent)	4
	Moderate assist (≥ 50% independent)	3
Complete dependenc on a helper	Maximal assist (≥ 25% independence)	2
	Total assist (< 25% independence)	1

34.1. References

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35. Differential diagnosis

This section contains differential diagnoses[A] **(DDx)** grouped either by signs and symptoms (*see below*), or by location/finding (starting on page 1209). DDx that are better covered elsewhere in a section devoted primarily to that topic are listed in *Table 35-1*.

A. in general usage, the term *differential diagnosis* sometimes refers to conditions that may mimic the one under consideration, however, it may also denote possible *etiologies* of a particular condition or finding. No attempt is made herein to consistently distinguish between these two similar usages of the term, although whenever possible, the word *etiologies* is employed where appropriate

Table 35-1 Differential diagnoses covered outside this chapter (followed by page number where the item may be found)

abducens palsy - 836	gyral enhancement - 1013	retinal hemorrhage - 919
anisocoria - 831	hydrocephalus - 311	sarcoidosis - 72
ankylosing spondylitis - 502	internuclear ophthalmoplegia - 834	seizures new onset, adult - 396
bladder dysfunction - 117	lateral disc herniation - 454	new onset, peds - 397
brachial plexopathy - 794	Meniere's disease - 842	nonepileptic - 400
carpal tunnel syndrome - 809	meralgia paresthetica - 819	status epilepticus - 403
cervical stenosis - *see below* & 489	multiple sclerosis - 62	schizencephaly - 243
chordomas - 676	ophthalmoplegia painful - 836	spinal cord tumors - 728
coma - 280	painless - 837	spinal epidural abscess - 377
Creutzfeldt-Jakob disease - 363	papilledema - 829	spinal stenosis lumbar - 478
dementia - 56	Parinaud's syndrome - 114	synovial cyst (spinal) - 456
diabetes insipidus - 15	Parkinson's disease - 60	thoracic outlet syndrome - 823
dizziness - 840	pineal region tumors - 691	torticollis - 541
extra-axial fluid (peds) - 904	pneumocephalus - 890	trigeminal neuralgia - 552
facial nerve palsy (Bell's palsy) - 844	prolactin elevation - 644	urinary retention - 118
giant cell arteritis - 74	pseudotumor cerebri - 716	vertigo - 840
Guillain-Barré - 68		

35.1. Differential diagnosis (DDx) by signs and

symptoms

35.1.1. Myelopathy

Items marked with a dagger (†) may present as a spinal epidural mass.

1. congenital
   A. (Arnold)-Chiari malformation: Type I often presents in early adulthood (*see page 488*)
   B. tethered cord: often may not present until after some trauma
   C. syringomyelia: may be congenital or post-traumatic in quadriplegics, usually presents with a central cord syndrome (see *Syringomyelia*, page 510) or progressive myelopathy
   D. neurenteric cyst: *see page 227*
   E. cord compression that occurs with some mucopolysaccharidoses: e.g. Morquio syndrome (due to atlanto-axial subluxation), Hurler syndrome
   F. hereditary spastic paraplegia: family history is key. Diagnosis of exclusion[1]
2. acquired
   A. cervical or thoracic spinal stenosis: often degenerative disease superimposed on congenitally narrow canal (congenital narrowing is frequent in achondroplastic dwarfs)
   B. traumatic: including spinal shock, hematomyelia, spinal epidural hematoma (see *vascular* below), barotrauma, electrical injuries, compression by bone fracture†. May follow minor trauma in the setting of spinal stenosis
   C. herniated intervertebral disc†: myelopathy more common in thoracic region, radiculopathy more common in cervical region (long tract signs are rare with herniated cervical disc)
   D. kyphosis
   E. extramedullary hematopoeisis†: hypertrophy of marrow → cord compression. Primarily in chronic anemias (e.g. thalassemia major) (*see page 43*)
   F. bony compression secondary to incompetence of odontoid process or transverse atlantal ligament†. May be congenital, traumatic (*see page*

963), neo-plastic, or inflammatory (especially rheumatoid arthritis)

G. epidural lipomatosis[†]: hypertrophy of epidural fat most often due to years of exogenous steroid therapy[2] - *see page 516*

H. ossification of the posterior longitudinal ligament **(OPLL)**[3] (*see page 504*)

I. arachnoiditis ossificans: a rare condition (only ≈ 43 case reports[4]) involving calcification of the arachnoid membrane. In the T-spine, may occur as ossified plaques or in a cylindrical form surrounding the spinal cord. May be difficult to detect on MRI and myelography. Plain unenhanced CT may be optimal for diagnosis

J. vertebral Paget's disease[†] (*see page 500*)

K. idiopathic spinal cord herniation[5, 6]: rare. Thoracic spinal cord herniates through an anterior dural defect frequently producing a Brown-Séquard syndrome or spastic paraparesis (*see page 514*)

3. neoplastic
   A. spine/spinal cord tumors (*see page 728* for details)[†]
      1. extradural (55%):
         a. primary tumors (rare) include: neurofibromas, chordomas, osteoid osteoma, aneurysmal bone cyst, vertebral hemangioma[7]
         b. if age > 40 yrs, suspect extradural lymphoma (primary or secondary) or leukemic deposits (chloroma), especially with pre-existing diagnosis of hematopoietic or lymphatic disorder
         c. epidural metastases become increasingly common after age 50 yrs. Occurs in up to 10% of cancer patients. 5-10% of malignancies present initially with cord compression (*see page 742*)
      2. intradural-extramedullary (40%): meningiomas, neurofibromas
      3. intradural-intramedullary: primary cord tumors (ependymoma, astrocytoma) and rarely intramedullary mets (*see page 730*)
   B. carcinomatous meningitis: neurologic deficit usually cannot be localized to a single level (*see page 711*)
   C. paraneoplastic syndrome: including effects on spinal cord or on peripheral nerves
4. vascular
   A. hematoma/hemorrhage
      1. spinal epidural hematoma[†]: usually associated with anticoagulation therapy[8] (*see page 515* and *page 39*)

a. traumatic: following LP or epidural anesthesia (*see page 39*)
b. spontaneous[9]: rare. Includes hemorrhage from spinal cord AVM (*see page 507*) or from vertebral hemangioma (*see page 738*)

2. spinal subarachnoid hemorrhage: as in spinal epidural hematoma (*see above*), this may also be post-traumatic (e.g. following LP[10, 11]) or secondary to spinal cord AVM
3. spinal subdural hematoma
4. hematomyelia

B. spinal cord infarction: uncommon with the elimination of syphilitic endarteritis. Most often in the territory of the anterior spinal artery, sparing posterior columns. Most commonly ≈ T4 level (watershed zone)
   1. atherosclerosis of radicular artery in elderly patient with hypotension is now the major cause of this rare condition
   2. clamping aorta during surgery (e.g. for abdominal aortic aneurysm)
   3. hypotension (relative or absolute) during surgery in the sitting position in the presence of spinal stenosis[12]. May be improved by avoiding absolute hypotension, using awake fiber-optic intubation and positioning, intraoperative SSEP monitoring and inducing hypertension if changes occur with positioning, avoidance of sitting position, and avoiding hyperflexion, hyperextension and traction
   4. aortic dissection
   5. embolization of spinal arteries

C. spinal cord vascular malformations (*see page 507*)[†]: 10-20% present as sudden onset of myelopathy usually in patients < 30 yrs[13], myelopathy may be secondary to:
   1. mass effect from AVM: spinal AVMs account for < 5% of lesions presenting as cord "tumors"
   2. rupture → SAH, hematomyelia, or epidural hematoma
   3. watershed infarction due to "steal"
   4. spontaneous thrombosis (necrotizing myelopathy of **Foix-Alajouanine** disease[14]): presents as spastic → flaccid paraplegia, with ascending sensory level

D. radiation myelopathy: due to microvascular occlusion (*see page 772*)

E. secondary to iodinated contrast material used for mesenteric or aortic angiography. Especially when angiogrammed in presence of hypotension, where cardiac output is shunted away from viscera and

into spinal radicular arteries. Treatment: place patient sitting, remove ≥ 100 ml of CSF via LP and replace with equal amount of saline over 30 mins[15]

5. autoimmune
   A. post-viral (or post-vaccination): may be etiology of autoimmune process (i.e. transverse myelitis). Viral prodrome present in ≈ 37% of cases of ATM. Viral infection is usually most damaging to gray matter (e.g. poliomyelitis)
6. demyelinating
   A. acute (idiopathic) **transverse myelitis (ATM)** (*see* *page 69*). Peak incidence during first 2 decades of life. Abrupt onset of LE weakness, sensory loss, back pain, and sphincter disturbance indistinguishable from spinal cord compression. Thoracic region most common. CT and myelogram are normal. MRI may demonstrate. CSF → pleocytosis and hyperproteinemia
   B. multiple sclerosis **(MS)**: diagnosed in only 7% of patients presenting as acute transverse myelopathy. Although more common in young adults, MS can occur at any time in life. Myelopathy of MS is usually insidious, and is usually incomplete (i.e. some sparing). Affects myelin, thus sparing gray matter. Abdominal cutaneous reflexes are almost always absent in MS
   C. **Devic syndrome** (neuromyelitis optica **(NMO)**): a variant of MS characterized by acute bilateral optic neuritis and transverse myelitis (extending ≥ 3 levels[16], often causing cervical myelopathy). Spinal cord edema may become so severe as to cause complete block on myelography. More common in Asia and India than U.S. or Europe. Compared to classic MS: the myelopathy tends to be more severe (pathology: more necrosis as opposed to incomplete demyelination) and with less chance of recovery. Distinct serum IgG antibodies (NMO-IgG) may help differentiate from MS[17]
7. metabolic/toxic
   A. (subacute) **combined system disease (CSD)** (AKA subacute combined columnal degeneration): due to vitamin B_{12} (cyanocobalamin) deficiency.
      1. etiologies:
         a. dietary deficiency of B_{12}
         b. **pernicious anemia**: malabsorption of B_{12} in the distal ileum due

to lack of secretion of intrinsic factor (a small polypeptide) by gastric parietal cells[18])

c. other gastric disorders: low gastric pH e.g. in Zollinger-Ellison syndrome can inhibit attachment of intrinsic factor to ileal receptors

2. clinical: onset is gradual and uniform. Begins with symmetrical paresthesias in feet or hands (posterior column involvement) → leg stiffness, weakness, and proprioceptive deficits with unsteadiness that is worse in the dark → spasticity → paraplegia → bowel and bladder dysfunction. Dementia (confusion, memory impairment, irritability…) occurs in advanced cases due to cerebral white matter changes. Visual disturbances with or without optic atrophy may be due to optic nerve demyelination

3. labs:

a. serum B_{12}: the most sensitive test. However, normal B_{12} levels do not R/O B_{12} deficiency. If there are neurologic symptoms then check malonic acid or other markers of B_{12} deficiency such as methylmalonic acid (also check homocysteine to R/O folate deficiency)

b. CBC: most (but not all) patients will have a <u>macrocytic</u> anemia (folic acid deficiency also produces megaloblastic anemia. Folic acid corrects the anemia, even with CSD, but <u>not</u> the neurologic deficits which may actually worsen)

c. <u>Schilling test</u>: determines the cause of the B_{12} deficiency even if B_{12} injections have already been given

4. imaging: T2WI MRI may demonstrate increased signal within the white matter of the spinal cord, predominantly in the posterior columns but may also be seen in spinothalamic tracts

5. treatment: B_{12} injections or large doses of oral preparations[19]

B. toxins: local anesthetics used for spinal anesthesia rarely cause myelopathy

8. infectious

A. (para) spinal abscess (AKA <u>spinal epidural abscess</u>) or epidural empyema[†]: often history of staphylococcus infection, usually a skin furuncle. Vertebral osteomyelitis often accompanies[20]. Produces local tenderness, back pain, fever, elevated ESR (*see page 376*)

B. vertebral osteitis/osteomyelitis[†] (*see page 380*)

C. pyogenic discitis[†]: spontaneous or following procedures (*see* *page 383*)

D. HIV or AIDS related myelopathy: similar to B_{12} deficiency. Spastic weakness & ataxia. Can cause vacuolization of spinal cord. "**Tropical (spastic) paraparesis of AIDS**" also seen in HTLV-I infection[21]

E. tuberculosis: Pott's disease, see *Tuberculous vertebral osteomyelitis*, page 381

F. spinal meningitis with pachymeningitis

G. viral:

1. herpes varicella-zoster: rarely causes necrotizing myelopathy
2. Herpes simplex type 2: may cause ascending myelitis
3. cytomegalovirus: may cause transverse myelitis

H. syphilitic involvement: may cause tabes dorsalis, syphilitic meningomyelitis, or spinal vascular syphilis. Diagnosed by serum and CSF serology

I. parasitic cysts[†]

J. some forms of Creutzfeldt-Jakob disease (CJD) with predominant initial muscle wasting may mimic spinal cord disease or ALS (*see* *page 362*)

9. peripheral neuromuscular disorder

A. Guillain-Barré syndrome **(GBS)**: rapidly ascending weakness (mimics cord compression) with areflexia and near normal sensation (*see* *page 66*)

B. chronic dysimmune neuropathies: presumed to be immune mediated[22]

1. chronic immune demyelinating polyradiculoneuropathy (CIDP): similar to GBS but can progress over a longer period of time (*see* *page 68*)
2. multifocal motor neuropathy **(MMN)**: characterized by asymmetric muscle wasting, cramping & LE twitching. May mimic ALS, but is treatable (with IVIg or immunosuppression)

C. myopathies: including steroid myopathy (usually affects proximal > distal muscles)

10. motor neuron diseases

A. **amyotrophic lateral sclerosis (ALS)**: upper and lower motor neuron disease. <u>Slight</u> spasticity of LEs (extreme spasticity is rare), atrophic weakness of the hands and forearms, fasciculations in the UEs, absence of sensory changes (including lack of pain), sphincter control

usually preserved (*see page 65*)

B. primary lateral sclerosis: age > 50. No LMN signs. Slower progression than ALS (yrs to decades). Pseudobulbar palsy is common[23] (*see page 65*)

† items with dagger may also present as a spinal epidural mass

35.1.2. Sciatica

Definition: pain in the distribution of the sciatic nerve. The sciatic nerve is comprised of components of nerve roots of L4-S3. The nerve passes out of the pelvis through the greater sciatic foramen along the back of the thigh. In the lower third of the thigh it divides into the tibial and common peroneal nerves.

The most common cause of sciatica is radiculopathy due to a herniated lumbar disc[24]. The differential diagnosis is similar to that for myelopathy (*see above*) but also includes:

1. congenital
   - A. meningeal cyst (perineural cyst) (see *Spinal meningeal cysts*, page 509)
   - B. conjoined nerve root: (*see page 256*) initially dismissed as a possible cause of radiculopathy, but current thinking recognizes that these may be symptomatic possibly by tethering
2. acquired
   - A. spinal stenosis/spondylosis/spondylolysis/spondylolisthesis
   - B. juxtafacet cyst: includes synovial cyst and ganglion cyst[25]: detection is increasing with the use of MRI (*see page 456*)
   - C. nerve root sheath cyst: may arise near axilla of nerve root and cause compression of adjacent roots. Treatment: excise cyst and oversew the ostium
   - D. arachnoiditis ossificans: rare (*see page 1186*). In the lumbar region may occur as columnar, cylindrical, or irregularly shaped masses[26]. May produce low back pain, radiculopathy, or cauda equina syndrome
   - E. heterotopic ossification around the hip[27]
   - F. injection injuries from misplaced IM injections
   - G. compartment syndrome of the posterior thigh
   - H. injury complicating total hip arthroplasty[28]
   - I. radiation injury following treatment of nearby tumors

3. infectious
   A. discitis: usually causes excruciating pain with any movement (*see page 383*)
   B. Lyme disease: *see page 368*
   C. herpes zoster: a rare cause of radiculopathy[29]. Lumbosacral dermatomes are involved in ≈ 10-15% of zoster cases. Pain is usually independent of position. Typical herpetic skin lesions usually follow onset of pain by 3-5 days. 1-5% develop motor weakness (usually in arms or trunk). Sacral zoster can cause detrusor paralysis, producing urinary retention. 55% of those with motor symptoms have good recovery, 30% have fair to good recovery
4. neoplastic:
   A. spine tumors: multiple myeloma (*see page 740*), metastases (*see page 742*)…
   B. bone or soft-tissue tumors along the course of the sciatic nerve: may result in erroneous laminectomy for herniated lumbar disc[30]. Pain is usually <u>insidious</u> in onset, and <u>not positional</u> (*see below*)
      1. intraabdominal or pelvic neoplasm
      2. tumors of the thigh
      3. tumors in the popliteal fossa or calf
5. inflammatory:
   A. trochanteric bursitis: may produce pseudoradiculopathy. Rarely extends to the posterior thigh or as far distally as the knee (*see page 479*)
   B. myositis ossificans of the biceps femoris muscle[31]
6. vascular:
   A. sciatica may be mimicked by intermittent (i.e. vascular) claudication
   B. psoas hematoma: usually in patient on anticoagulant. Sometimes drainage is required
7. referred pain of nonspinal origin: not dermatomal. Nerve root tensions signs (*see page 443*) are usually negative. Includes:
   A. pyelonephritis
   B. renolithiasis including ureteral obstruction
   C. cholecystitis
   D. appendicitis
   E. endometritis/endometriosis
   F. posterior perforating duodenal ulcer

G. inguinal hernia, especially if incarcerated

H. aortic dissection: *see page 1192*

8. **piriformis syndrome (PS)**: controversial. Piriformis muscle originates on anterior S2-4 VBs, sacrotuberous ligament and passes through the greater sciatic notch to attach to the greater trochanter of the femur. It is innervated by L5-S1. It is the principle external rotator of the extended hip. It may irritate or compress the sciatic nerve (AKA pseudosciatica, can mimic symptoms of a herniated disc). The superior gluteal nerve is spared as it has a take-off proximal to the muscle. Conversely, PS may occur *secondary* to lower lumbar radiculopathy. Produces pain in the sciatic distribution and weakness of external rotation and abduction of the hip. Signs: **Freiberg test** (pain with forced internal rotation of the hip with thigh extension) or the Pace test (pain on resisted abduction/external rotation of the hip). No well designed studies of treatments. Advocated therapies include: PT, stretching, injection of the muscle localized by digital rectal exam taking care not to inject the sciatic nerve itself & piriformis muscle section. Sometimes long-lasting relief can follow injection with local anesthetic. Use of botulinum toxin (Botox®) injections has been described
9. more peripheral involvement (i.e. neuropathy) that may be confused with radiculopathy. Including:

A. femoral neuropathy mistaken for L4 radiculopathy (*see below*)

B. proximal sacral plexus lesion mistaken for S1 radiculopathy (*see below*)

C. diabetic neuropathy (*see page 796*) including diabetic amyotrophy

D. tumors (*see below*)

EXTRASPINAL TUMORS CAUSING SCIATICA

★ **Pain characteristics**: pain is almost always insidious in onset[30]. It may be intermittent initially, but eventually all patients develop pain that is constant, progressive and unaffected by position or rest[30]. Significant night pain is described in ≈ 80%.

Straight leg raising was positive in most, but in more than half the pain was localized to a specific point along the course of the nerve, distal to the sciatic notch[30]. Conservative treatment brings either no or only temporary relief.

Approximately 20% will have a previous history of tumor (usually neurofibromatosis or previous malignancy). Malignancies include[30]: metastatic lesions, primary bone sarcomas (chondrosarcoma…), soft-tissue sarcomas

(liposarcoma…). Benign tumors include: lipoma, neurofibroma, schwannoma, aneurysmal bone cyst of the sacrum, giant cell tumor of the sacrum (*see page 742*), tenosynovial giant cell tumor.

In two-thirds of cases, a detailed medical history and physical exam allowed localization and even determining the nature (bone tumor vs. soft-tissue) of the lesion[30]. Radiographs that show the entire pelvis and the proximal femur will demonstrate almost all tumors in these locations[30, 32].

FEATURES DIFFERENTIATING RADICULOPATHY IN SCIATICA

Sciatica may result from nerve root involvement within the spinal canal (e.g. with lumbar disc herniation). Clinically this produces a nerve root syndrome (see *Nerve root syndromes*, page 445). Spinal imaging studies (MRI, myelogram/CT) will usually detect nerve root compression here. More peripheral involvement may be difficult to image.

L4 involvement

Femoral neuropathy is often mistakenly identified as an L4 radiculopathy. Distinguishing features are shown in *Table 35-2*.

L5 involvement

Peroneal nerve palsy may be mistaken for L5 radiculopathy (see *Foot drop*, page 1194).

S1 involvement

Outside the spinal canal, S1 can also be involved as it enters the sacral plexus, e.g. by a pelvic tumor. In plexus lesions, EMG will show sparing of the paraspinal muscles (these nerves exit in the region of the neural foramen) and the gluteus maximus and medius (superior and inferior gluteal nerves take-off just distal to the paraspinal nerves).

Table 35-2 Distinguishing femoral neuropathy from L4 radiculopathy

Feature	Femoral neuropathy	L4 radiculopathy
Sensory loss		
distribution (see *Figure 5-13*, page 94)	anterior thigh	dermatome from ≈ knee to medial malleolus, spares anterior thigh
Muscle weakness		

iliopsoas	weak	normal
thigh adductors	normal (innervated by obturator nerve)	may be weak
quadriceps	weak	weak

35.1.3. Acute paraplegia or quadriplegia

Entities causing **spinal cord compression** usually present as: paraplegia or -paresis (or quadriplegia/paresis), urinary retention (may require checking post-void residual to detect), and impaired sensation below level of compression. May develop over hours or days. Reflexes may be hyper- or hypoactive. There may or may not be a Babinski sign. Excluding trauma, the most common cause is compression by tumor or bone.

Etiologies

Some overlap with myelopathy. For items with asterisk, see *Myelopathy*, page 1185:

1. in infancy (may produce “floppy infant syndrome”)
   A. spinal muscular atrophy (the most severe form is called **Werdnig-Hoffmann** disease and is usually fatal within months): autosomal recessive congenital disease of childhood with degeneration of anterior horn cells. Only rarely evident at birth (where it presents as a paucity of movement), produces weakness, areflexia, muscle and tongue fasciculations with normal sensation. Severe cases progress over the first year or two to quadriplegia
   B. spinal cord injury during parturition: a rare sequela of breech delivery
   C. congenital myopathies: e.g. infantile acid maltase deficiency (Pompe disease)
   D. infantile botulism: ileus, hypotonia, weakness, mydriasis, *Claustridium botulinum* bacteria and toxin in feces
2. traumatic spinal cord injury
   A. major trauma: diagnosis is usually evident
   B. minor trauma: may cause cord injury in setting of spinal stenosis, may → central cord syndrome (see *Central cord syndrome*, page 948)
   C. atlantoaxial dislocation: from major trauma or due to instability from tumor or rheumatoid arthritis (*see page 495*)

3. congenital
   A. extradural spinal cord compression by bone secondary to cervical hemivertebra (symptoms not present at birth, may develop decades later, occasionally after minor trauma)
   B. cervical stenosis (usually with superimposed spondylosis): quadriplegia or central cord syndrome may follow minor trauma (*see page 948*)
   C. achondroplastic dwarfism: spinal stenosis (animal model: dachshund)
   D. syringomyelia: usually presents with central cord syndrome
4. metabolic
   A. combined system disease*: *see page 1187*
   B. thallium poisoning: usually causes sensory and autonomic symptoms, quadriplegia and dysarthria may be seen in severe cases
   C. central pontine myelinolysis: *see page 11*
5. infectious
   A. epidural spinal infection (abscess or empyema)*
   B. post-viral (or post-vaccination): may be a transverse myelitis*
6. peripheral neuromuscular disorder*
   A. Guillain-Barré syndrome: classically an <u>ascending</u> paralysis (*see page 66*), but paraparesis mimicking a spinal cord lesion is an unusual variant[33]
   B. myopathies
7. neoplastic*: spinal cord tumors
8. autoimmune*
9. vascular
   A. acute pontomedullary infarction: age usually > 50 yrs. Patient is quadriplegic, alert, with bulbar palsies (eye movement abnormalities, impaired gag and speech)
   B. spinal cord infarction*: including AVM, radiation myelopathy…
10. miscellaneous compressive*: including epidural hematoma, bony compression, epidural lipomatosis
11. functional: hysteria, malingering
12. bilateral cerebral hemisphere lesion (involving both motor strips): e.g. post-cerebral irradiation or parasagittal lesion. Will not have sensory <u>level</u>

* for items with asterisk, see *Myelopathy*, page 1185 for details

35.1.4. Hemiparesis or hemiplegia

May be produced by anything that interrupts the corticospinal tract from its origin in the pyramidal cells of Betz in the motor strip down to the cervical spine. This results an upper motor neuron paralysis (see *Table 24-3*, page 786) which should also produce long tract findings, including Babinski sign ipsilateral to hemiplegia. Etiologies include:

1. lesions of the cerebral hemisphere in the region of the contralateral motor strip. Large lesions may also involve sensory cortex producing reduced sensation ipsilateral to the hemiparesis
   A. tumor (neoplasm): primary or metastatic
   B. traumatic: epidural or subdural hematoma, hemorrhagic contusion of the brain, compression by depressed skull fracture
   C. vascular:
      1. infarction
         a. ischemic: embolic, low flow (due to atherosclerosis, arterial dissection…)
         b. hemorrhagic: intracerebral hemorrhage, aneurysmal SAH…
      2. TIA (*see page 1010*)
   D. infection: cerebritis, abscess
2. lesions of the contralateral internal capsule: produces pure motor hemiplegia without sensory loss. Most common etiology is ischemic lacunar infarct
3. lesions of the brainstem: ischemic infarct, hemorrhage, tumor
4. lesions of cervicomedullary junction: foramen magnum lesions (*see page 1212*)
5. unilateral spinal cord lesions above ≈ C5 ipsilateral to the weakness producing a Brown-Séquard syndrome with *contralateral* sensory loss to pain and temperature (*see page 950*). For etiologies, *see page 951*
6. hypoglycemia can sometimes be associated with hemiparesis that clears after administration of glucose

In a patient with unexplained hemiparesis/hemiplegia, especially after trauma, consider carotid dissection.

35.1.5. Low back pain

The following considers primarily low back pain **(LBP)** without radiculopathy or myelopathy, although some overlap occurs. Trauma is usually obvious and is not discussed. See *Sciatica* on page 1188 for differential diagnosis of that and also *Low back pain and radiculopathy* on page 428 for evaluation.

ACUTE LOW BACK PAIN

Similar to list for myelopathy (*see page 1185*). Most cases are non-specific (e.g. **lumbosacral sprain**), only 10-20% can be given a precise pathoanatomical diagnosis[34]:

1. patients writhing in pain should be evaluated for an intraabdominal or vascular condition (e.g. pain of aortic dissection is typically described as a "tearing" pain): patients with neurogenic LBP tend to remain as still as possible, possibly needing to change positions at intervals
2. unrelenting pain at rest:
   A. spinal tumor (intradural or extradural) (*see page 728*)
      1. primary or metastatic spine tumor: suspected in patients with pain duration > 1 month, unrelieved by bed rest, failure to improve with conservative therapy, unexplained weight loss, age > 50 yrs[35]
      2. nocturnal back pain relieved by aspirin is suggestive of osteoid osteoma or benign osteoblastoma[36] (*see page 736*)

   B. infection (especially in IV drug abusers, diabetics, post spinal surgery, immunosuppressed patients, or those with pyelonephritis or UTI post-GU surgery). Fever is somewhat insensitive for spinal infections. Spine tenderness to percussion has 86% sensitivity with bacterial infections, but a low specificity of 60%[35]. Types of infections include:
      1. discitis
      2. spinal epidural abscess: should be considered in patients with back pain, fever, spine tenderness, or skin infection (furuncle)
      3. vertebral osteomyelitis

   C. inflammatory:

   D. **sacroiliitis**: may produce pain and tenderness over one or both SI joints
      1. pelvic x-rays may show sclerosis of one or both sacroiliac joints
         a. bilateral & symmetric
            i. **ankylosing spondylitis** (*see page 502*): morning back stiffness, no relief at rest, improvement with exercise[37]. Usually seen in males with symptom onset before age 40 yrs.

Positive **Patrick's test** (*see page 444*) and pain on compressing the pelvis with the patient in the lateral decubitus position

ii. Reiter syndrome: a reactive arthritis (usually 1-3 weeks following certain bacterial infections) with involvement of at least one other non-joint area (urethritis, uveitis/conjunctivitis, skin lesions, mucosal ulcerations…). 75% are HLA-B27 positive

iii. may occur in Crohn's disease

b. bilateral & asymmetric

i. psoriatic arthritis

ii. rheumatoid arthritis: adult & juvenile forms

c. unilateral

i. gout

ii. osteoarthritis

iii. infection

3. evolving neurologic deficit (**cauda equina syndrome**: perineal anesthesia, urinary incontinence or urgency or retention, progressive weakness) all require emergent diagnostic evaluation to rule-out treatable conditions such as:

   A. spinal epidural abscess: *see page 376*

   B. spinal epidural hematoma: *see page 515*

   C. spinal tumor (intradural or extradural): *see page 728*

   D. massive central disc herniation: *see page 446*

4. pathologic fracture: acute pain in patients at risk for osteoporosis or with known Ca should prompt evaluation for pathologic fractures

   A. lumbar compression fracture: see *Osteoporotic spine fractures*, page 992

   B. sacral insufficiency fracture[38]: especially in rheumatoid arthritis patients on chronic steroids, often with no antecedent history of trauma. May cause back pain and/or radiculopathy. Often missed on plain films, best seen on CT, but may also be detected on bone scan

5. coccydynia: pain and tenderness around the coccyx (*see page 516*)

6. tears in the anulus fibrosus ("anular tears")[39] (NB: also present in 40% of asymptomatic patients between 50-60 yrs age, and 75% between 60-70 yrs[40])

7. rarely following subarachnoid hemorrhage **(SAH)** due to irritation of

lumbar nerve roots and dura: usually accompanied by other signs of SAH (*see* *page 1035*)

8. myalgia: may be a side-effect of "statins" (drugs used to lower serum concentration of LDL cholesterol), sometimes with accompanying weakness and rarely with severe rhabdomyolysis and myoglobinuria leading to renal failure (risk may be increased with renal or hepatic dysfunction, advanced age, hypothyroidism, or serious infection)[41]
9. drug induced
   A. statins: *see above* under myalgia
   B. phosphodiesterase type 5 **(PDE5)** inhibitors used for erectile dysfunction: all may be associated with LBP, but the incidence is higher with tadalafil[42], etiology unknown. Usually occurs 12-24 hours post-dose and resolves by 48 hours. Most respond to simple analgesics

SUBACUTE LOW BACK PAIN

10% have LBP that persists > 6 weeks.

Differential diagnosis

Includes causes of acute LBP (above) and also:

1. continued pain at rest should prompt evaluation for spinal osteomyelitis (especially with fever and elevated ESR) or neoplasm if not already done
2. plain spine x-rays may show possibly causative conditions, although many or all of the following may also be seen in asymptomatic patients
   A. spondylolisthesis (*see* *page 475*)
   B. spinal osteophytes
   C. lumbar stenosis
   D. **Schmorl's node** or **nodule**: disc herniation through cartilaginous end-plate into vertebral body (NB: may also be seen in 19% of asymptomatic patients[43]) (*see* *page 455*)

CHRONIC LOW BACK PAIN

After 3 months, only ≈ 5% of patients will continue to have persistent symptoms. A structural diagnosis is possible in only ≈ 50% of these patients. These patients account for 85% of the cost in lost work and compensation[34]. Differential diagnosis includes causes of acute and subacute LBP listed above, as well as:

1. degenerative conditions
   A. degenerative spondylolisthesis (*see page 475*)
   B. spinal stenosis (affecting the spinal canal)
   C. lateral recess syndrome
2. spondyloarthropathies
   A. ankylosing spondylitis: look for erosive changes adjacent to SI joint and positive test for HLA-B27 antigen
   B. Paget's disease of the spine: vertebral involvement is very common in a patients with Paget's disease
3. osteitis condensans ilii: increased density in ilium, usually asymptomatic (incidental) finding. Occasionally may produce low back pain or tenderness. Usually found in women who have been pregnant
4. psychological overlay: including secondary gain (financial, emotional…)

35.1.6. Foot drop

Key concepts:

> • weak anterior tibialis (foot extension) innervated by deep peroneal nerve (L**4**, 5)
> • most common etiologies: L4/L5 radiculopathy, common peroneal nerve palsy
> • in a patient with foot drop, check posterior tibialis (foot inversion) and gluteus medius (internal rotation of flexed hip) - both are spared in peroneal nerve palsy and both should be involved with L4/5 radiculopathy
> • EMG can assist in localization and prognostication

Definition: weakness of anterior tibialis (primarily L4 and to a lesser extent L5), often accompanied by a weak extensor digitorum longus and extensor hallicus longus (primarily L5 with some S1 contribution), all of which are innervated by the deep peroneal nerve.

With common peroneal nerve **(CPN)** palsy, there is sparing of posterior tibialis (foot inversion, innervated by posterior tibial nerve) and gluteus medius (internal rotation of the thigh with the hip flexed, innervated by superior gluteal nerve, primarily L5 with some L4, the takeoff is shortly after the roots exit from neural foramen). With L4 or L5 root lesions these muscles will also be

weak, *see Table 35-4*. **Flail foot** results from paralysis of dorsiflexors plus plantarflexors, e.g. in sciatic nerve dysfunction as can occur during surgery for hip fracture/dislocation[44] or injection injuries (IM injections should be give superiorly and laterally to a line drawn between the posterior superior iliac spine and the greater trochanter of the hip). NB: the pero-neal division of the sciatic nerve tends to be more vulnerable to injury than the tibial division.

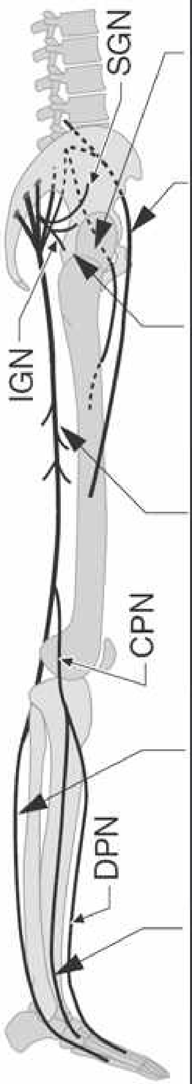
Table 35-3 Localization of lesion with foot drop

Lesion	Motor deficit*					Sensory changes
	anterior tibialis (**L4**, 5 ankle dorsiflexion)	peroneus longus/brevis (L5, S1 foot eversion)	tibialis posterior (L4, 5 foot inversion)	biceps femoris (L5, **S1**, 2 knee flexion)	gastrocnemius (**S1**, 2 plantarflexion)	
deep peroneal nerve	x					minimal, or great toe web space
superficial pero-neal nerve		x				lateral distal leg and dorsum of foot
common peroneal nerve (CPN)	x	x				all of the above
L4 or L5 radiculopathy	x	x	x			dermatomal (see *Fig-ure 5-13*, page 94)
peroneal division of sciatic nerve†	x	x	x	x		as with common per-oneal
main trunk of sci-atic nerve	x	x	x	x	x	lateral distal leg and entire foot

* **x** denotes that the indicated muscle is involved (i.e. weak)

† see footnote *2 under *Table 35-4*

Table 35-4 Physical exam to localize the lesion in a patient with LE weakness



Muscle to check	Rationale	Findings: exam
thigh adductors (adductors longus, brevis and magnus) (**L2**, **L3**): innervated by the **obturator nerve**	involvement indicates that the lesion includes more than sciatic nerve/L5 root (e.g. paravertebral mass, cauda equina lesion if bilateral findings)	weakness when adducting thigh while supine with knee extended
quadriceps femoris innervated by the **femoral nerve**	(same as above)	weakness of knee extension (L2, **L3**, **L4**)
muscles innervated by **L5 branches** that exit the lumbar plexus very close to the neural foramina	involvement indicates very proximal lesion (e.g. nerve root or very proximal (paravertebral) lumbar plexus)*1	weakness of: 1. gluteus medius (**L4**, **L5**, S1): internally rotate thigh 2. gluteus maximus (**L5**, **S1**, 2): dig heel into bed while supine
L5 innervated muscles (via **sciatic nerve**) proximal to the takeoff of the common peroneal nerve*2	if muscles listed above are intact, involvement of muscles to the right localizes the lesion to sciatic nerve above mid thigh (e.g. injury to sciatic nerve at the greater sciatic notch)	1. slight weakness of biceps femoris (lateral hamstrings) (L5, **S1**, 2): flex the knee (with thigh flexed) 2. gastrocnemius weakness (foot plantarflexion) (this + foot drop = flail foot) unless injury only to peroneal division of sciatic nerve*2
muscles innervated by (posterior) **tibial nerve**	sparing of these with foot drop indicates lesion distal to takeoff of common peroneal nerve (foot drop with weak foot inversion may be L4 or 5 radiculopathy)	weakness of tibialis posterior (**L4**, **L5**): invert foot (foot should be plantarflexed to eliminate anterior tibialis)
anterior tibialis innervated by **deep peroneal nerve**	involvement does not narrow down etiology until other muscles are examined	weakness of ankle dorsiflexion (foot drop)
muscles innervated by **superficial peroneal nerve**	preservation of these with foot drop localizes the lesion to the deep peroneal nerve	weakness of the peroneus longus and brevis (L5, S1): evert the foot

*1 Note: EMG can differentiate root lesion from proximal plexus lesion by detecting involvement of paraspinal muscles which occurs in root but not in plexus lesions since dorsal rami exit proximal to plexus

*2 the peroneal division of the sciatic nerve is more vulnerable to injury than the tibial division for several reasons. It is thus not unusual to see isolated peroneal nerve injuries above the knee e.g. from hip dislocation or fractures, stab wounds, injection injuries…

Abbreviations

CPN = common peroneal nerve

DPN = deep peroneal nerve
IGN = inferior gluteal nerve
SGN = superior gluteal nerve

Etiologies of foot drop:
Three major categories: 1) muscular, 2) neurologic, 3) anatomic.

1. peripheral nerve palsies (more common) (*see Table 35-3* and *Table 35-4*)
   A. peroneal nerve injury (also, *see Common peroneal nerve palsy*, page 820 *for details including etiologies*). Branches that may be involved:
      1. deep peroneal nerve: isolated foot drop with minimal sensory loss (except possibly in great toe web space)
      2. superficial peroneal nerve: weakness of peroneus longus and brevis (foot eversion) with no foot drop. Sensory loss: lateral aspect of lower half of leg and foot
      3. common peroneal nerve: combination of above (i.e. foot drop + weak foot eversion, with sparing of tibialis posterior (foot inversion). Sensory loss: lateral aspect of lower half of leg and foot)
   B. L5 radiculopathy: (or, less commonly, L4). The most common cause is HLD at L4-5, other etiologies include: lumbar spinal stenosis at L4-5, sacral ala fracture (*see page 997*)
      - results in pain and/or sensory changes in L5 (or L4) dermatome
      - weakness with radiculopathy tends to be more pronounced in distal muscles (e.g. anterior tibialis) than in proximal (e.g. gluteus maximus)
      - painless foot drop is unlikely to be due to radiculopathy; consider peroneal neuropathy, diabetic neuropathy, lesion anywhere along pyramidal tract, motor neuron disease…
   C. lumbar plexus injury
   D. lumbosacral plexus neuropathy: *see page 795*
   E. injury to lateral trunk of sciatic nerve
   F. peripheral neuropathy: weakness tends to be greater distally, producing wrist or foot drop. Classic example: Charcot-Marie-Tooth (*see page 793*), findings tend to be rather dramatic in spite of the fact that it often doesn't seem to bother the patient very much
   G. early in the course of motor neuron disease (ALS)
   H. heavy metal poisoning

2. central nervous system causes (foot drop here is usually painless)
   A. cortical lesion (UMN): parasagittal lesions in region of motor strip (sensation will be spared if the lesion does not extend posteriorly to the sensory cortex)[45]. There may be a Babinski sign or hyperactive Achilles reflex (so-called "spastic foot drop"). Usually painless
   B. spinal cord injury: including cervical spinal myelopathy
3. non-neurogenic causes
   A. muscular dystrophy
   B. lead toxicity: in children may cause foot drop with no sensory loss
   C. anterior compartment syndrome

Clinical

Loss of dorsiflexion causes **foot slap** with the front of the foot when the heel strikes the ground while walking. Also during the swing phase of gait the front of the foot may snag the ground (especially on uneven surfaces) which may cause tripping; thus patients develop **steppage gait** (exaggerated thigh & knee flexion) on the affected side. Associated weakness of tibialis posterior, when present (e.g. with L5 radiculopathy) destabilizes the ankle permitting eversion which also predisposes to falls and to ankle fractures. Chronic foot drop may produce achilles tendon contracture with talipes equinus.

Wasting of the extensor digitorum brevis may be seen.

Laboratory evaluation

1. bloodwork: glucose, ESR
2. EMG: can help differentiate L5 radiculopathy from peroneal nerve palsy, plexus lesion (*see* Table 35-4) or motor neuron disease (*see* page 821 for details)

35.1.7. Weakness/atrophy of the hands/UEs

Hand/UE weakness or atrophy with relatively preserved function in the LEs.

1. cervical spondylosis: often causes sensory disturbance (*see* page 485)
2. cervical radiculopathy: *see* page 461
3. amyotrophic lateral sclerosis **(ALS)**: no sensory involvement. One of the few causes of clinically prominent fasciculations (*see* page 65 for details of ALS, *see* page 1188 for other distinguishing features, *see* page 786 for

fibrillations)

4. spinal cord pathology
   A. central cord syndrome: typically causes more involvement (weakness, sensory disturbance) in the UE than the LE (*see page 948*)
   B. syringomyelia: usually burning dysesthesias of the hands with dissociated sensory loss (*see page 510*)
5. brachial plexus injury: *see page 801*
6. brachial plexus neuropathy (includes Parsonage-Turner syndrome): *see page 794*
7. peripheral nerve problems, including
   A. carpal tunnel syndrome: *see page 808*
   B. ulnar neuropathy: *see page 812*
   C. other peripheral nerve entrapment syndromes: *see page 804*
8. foramen magnum lesions (*see page 1212*): can cause (Bell's) **cruciate paralysis**[46] due to compression above the pyramidal decussation which produces bilateral UE weakness and possibly atrophy of the hands with sparing of the LEs[47] (in the differential diagnosis for central cord syndrome). Compression on one side may produce the similarly named but clinically different **hemiplegia cruciata** (spastic palsy of one UE and the contralateral LE)[47]
9. thoracic outlet syndrome: *see page 822*
10. botulism: *see page 1202*
11. pharyngeal-cervical-brachial variant of Guillain-Barré syndrome: *see page 68*

ATROPHY OF THE FIRST DORSAL INTEROSSEOUS MUSCLE

Etiologies: either C8/T1 nerve root or ulnar nerve involvement (either may be focal or diffuse). There are 4 main differential diagnoses:

1. ulnar neuropathy: check median nerve to see if findings extend to a nearby but separate nerve
   A. at the elbow: *see page 813*
   B. at Guyon's canal: *see page 816*
2. nerve root involvement:
   A. cervical radiculopathy: C8 or T1
   B. nerve root avulsion: weakness + sensory loss with normal SNAP on EMG (*see page 270*) usually with a history of precipitating trauma

3. lower brachial plexus involvement
   A. thoracic outlet syndrome: *see page 822*
   B. Pancoast tumor: *see page 794*
4. neurodegenerative disorders
   A. amyotrophic lateral sclerosis (ALS): *see page 65*
   B. multifocal motor neuropathy (MMN): a chronic dysimmune neuropathy with asymmetric muscle wasting, cramping & LE twitching (*see page 1188*)

35.1.8. Radiculopathy, upper extremity (cervical)

See *Weakness/atrophy of the hands/UEs* above. In addition to those items:

1. primary shoulder pathology: characteristically, pain is aggravated by active and/or passive shoulder movement. In general, shoulder pathology does not produce pain referred to the neck
   A. rotator cuff tear
   B. bicipital tendonitis: tenderness over biceps tendon
   C. subacromial bursitis: there may be tenderness over the AC joint
   D. adhesive capsulitis
   E. impingement syndrome: the "empty can test" is usually positive (each arm held out in front, 30° lateral to straight forward, thumbs pointing down, as in emptying out a soda can. Examiner pushes down on the patient's hands while the patient resists. Test is positive if it reproduces pain)
2. shoulder pain is very common in polymyalgia rheumatica (*see page 77*), typically worsens with movement
3. interscapular pain: a common location for referred pain with cervical radiculopathy, may also occur with cholecystitis or some shoulder pathologies
4. MI: some cases of cervical radiculopathy (especially left C6) may present with symptoms that are suggestive of an acute myocardial infarction
5. complex regional pain syndrome AKA reflex sympathetic dystrophy: may be difficult to distinguish from cervical radiculopathy. Stellate ganglion blocks may help[48]. Also *see page 576*

35.1.9. Neck pain (cervical pain)

This section deals primarily with axial neck-pain without radicular features. For radicular features, see *Radiculopathy, upper extremity (cervical)* above.

1. cervical spondylosis (including facet arthritis)
2. cervical sprain: including whiplash associated disorder
3. fracture of the cervical spine: with upper cervical spine fractures (e.g. odontoid), patients characteristically hold their head in their hands, especially when going from recumbent to upright position
   A. traumatic
   B. pathologic (tumor invasion, rheumatoid arthritis)
4. occipital neuralgia: *see page 804*
5. herniated cervical disc:
   A. lateral herniated disc: if symptomatic, tends to produce more radicular symptoms in the UE than actual neck pain
   B. central disc herniation: if symptomatic, tends to produce myelopathy, does not produce any neck pain whatsoever in many cases
6. abnormalities of the craniocervical junction:
   A. Chiari 1 malformation: *see page 233*
   B. atlantoaxial subluxation
7. **fibromyalgia**: idiopathic chronic pain syndrome characterized by widespread nonarticular musculoskeletal pain, nodularity and stiffness[49, 50] without pathologic inflammation. Possible link to neuroendocrine dysfunction[51]. Afflicts 2% of the population[50], female:male ratio is 7:1. No diagnostic laboratory study. May be associated with psychiatric illness and multiple non-specific somatic complaints including malaise, fatigue, impaired sleep, GI complaints and cognitive impairment
8. Eagle's syndrome: elongation of the styloid process. Surgical resection can ameliorate the pain. Two variants:
   A. typical variant: history of tonsillectomy. Pharyngeal pain, dysphagia and otalgia
   B. second variant: AKA carotid artery-styloid process syndrome. Carotidynia radiating into ipsilateral eye and vertex

35.1.10. Burning hands/feet

1. spinal cord syndromes:
   A. central cord syndrome **(CCS)**: *see page 948*

   B. burning hands syndrome: a possible variant of CCS, described in football-related cervical spine injury (*see page 980*)
   C. numb-clumsy hand syndrome: seen in cervical myelopathy (*see page 488*)
2. complex regional pain syndrome **(CRPS)** AKA reflex sympathetic dystrophy: *see page 576*
3. peripheral neuropathy
   A. diabetic amyotrophy AKA Bruns-Garland syndrome: *see page 796*
4. **erythermalgia** AKA erythromelalgia: rare disorder characterized by erythema, edema, increased skin temperature, and burning pain of the hands and/or feet. Usually refractory to medical management, some success reported with epidural bipuvicaine[52], lidocaine patches[53], or cold soaks
   A. primary erythermalgia: etiology is idiopathic
   B. secondary erythermalgia: associated with autoimmune and rheumatologic factors
5. vascular:
   A. occlusive arterial disease: atherosclerosis, Raynaud's syndrome
   B. venous insufficiency

35.1.11. Muscle pain/tenderness

1. fibromyalgia: *see above*
2. myopathy
3. "statin" myopathy
4. diffuse severe sensitivity to light touch is a marker of nonorganic pain[54]

35.1.12. Lhermitte's sign

Really a symptom. Electrical shock-like sensation radiating down the spine usually provoked by neck flexion (shocks radiating up the spine are sometimes referred to as <u>reverse</u> Lhermitte's sign). Classically attributed to MS, but may occur in any process involving primarily the posterior columns.

Etiologies:

1. multiple sclerosis (MS): *see page 61*

2. cervical spondylosis
3. subacute combined degeneration: check for vitamin B_{12} deficiency (*see page 1187*)
4. cervical cord tumor
5. cervical disc herniation
6. radiation myelopathy: *see page 772*
7. Chiari type I malformation: *see page 233*
8. central cord syndrome: *see page 948*
9. SCIWORA (spinal cord injury without radiographic abnormality): *see page 974*

35.1.13. Encephalopathy

Many etiologies are similar to that for coma (*see page 280*). EEG may be helpful in distinguishing some etiologies (*see page 266*).

1. a rare cause may be (spontaneous) intracranial hypotension (*see page 305*)
2. hypertensive encephalopathy from malignant hypertension

35.1.14. Syncope and apoplexy

Syncope may be defined as one or more episodes of brief loss of consciousness **(LOC)** with prompt recovery (this term is considered by many to signify a vasovagal episode). The uncommonly used term **lipothymia** may be less likely to imply an etiology. Prevalence may be as high as ≈ 50% (higher in the elderly). **Apoplexy** is traditionally considered a form of hemorrhage, usually intracerebral. The recovery from apoplexy would therefore usually be slower than for syncope.

Etiologies (adapted[55, 56])

1. vascular: a few myotonic jerks may be seen in cerebral ischemia
    A. cerebrovascular
        1. subarachnoid hemorrhage (most commonly aneurysmal)
        2. intracerebral hemorrhage
        3. brain stem infarction
        4. pituitary apoplexy (rare): *see page 635*
        5. vertebrobasilar insufficiency **(VBI)**: *see page 1158*
        6. rarely with migraine

B. cardiovascular
   1. Stokes-Adams attacks: disorder of AV-node conduction in the heart resulting in syncope with bradycardia
   2. carotid sinus syncope: minimal stimulation (e.g. tight shirt collar, syncope while shaving…) causes reflex bradycardia with hypotension, more common in patients with carotid vascular disease. Bedside carotid massage with ECG and BP monitor may diagnose[56]
   3. cardiac standstill: seen rarely in patients with glossopharyngeal neuralgia (*see page 563*)
   4. vasodepressor syncope (the common **faint**), AKA vasovagal response, and recently AKA **neurocardiogenic syncope**[57]: the most common cause of transient LOC. Hypotension usually with any of the following autonomic manifestations: pallor, nausea, heavy perspiration, pupillary dilatation, bradycardia, hyperventilation, salivation. Usually benign. Most common in age < 35 yrs
   5. orthostatic hypotension: drop in SBP ≥ 25 mm Hg on standing
   6. triggered syncope: includes micturition, tussive syncope, weight lifting syncope… (most involve elevation of intrathoracic pressure)

2. infectious
   A. meningitis
   B. encephalitis
3. seizure: in general, there are involuntary movements and confusion afterwards, lasts at least several minutes. **Todd's paralysis** may follow and usually resolves slowly over a period of a few hours (*see page 396*). There may be irritative specialsense phenomena (visual, auditory, or olfactory hallucinations)
   A. generalized
   B. complex partial
   C. akinetic seizure
   D. drop attack (loss of posture without LOC): seen in Lennox-Gastaut
4. metabolic: hypoglycemia (may produce seizure, usually generalized)
5. miscellaneous
   A. intermittent ventricular obstruction: the classic example is a colloid cyst of the third ventricle, but this mechanism is questionable (*see page 665*)

B. narcoleptic cataplexy: narcolepsy is characterized by somnolence and sudden attacks of weakness (cataplexy) when awake. Easy arousal and lack of post-ictal drowsiness distinguishes cataplexy from a seizure

C. psychogenic

6. intracranial hypotension: usually with CSF shunt when upright (*see page 325*)
7. unknown: in ≈ 40% of cases no cause can be diagnosed

Practical approach to syncope

The core of diagnosis and management are the H&P, orthostatic vital signs, and the ECG, with a combined diagnostic yield of 50%[58] covering:

1. reflex mediated such as vasovagal or valsalva/stress-induced: 36 -62%
2. cardiac valvular etiology or arrhythmia: 10-30%
3. orthostatic due to autonomic dysregulation, dehydration or polypharmacy: 2-24%
4. cerebrovascular due to stroke: ≈ 1%
5. seizure

Evaluation:

1. history: includes

A. medication list: look for drugs that may cause orthostatic hypotension, especially blood pressure medication, beta blockers

B. precipitating factors: e.g. change in position, sensitivity to tight collars…

C. premonitory factors: e.g. sweating and tremulousness may signify hypoglycemia, bradycardia is associated with vasovagal events, tonic-clonic movements may occur with a seizure

D. post-ictal emergence: usually rapid after a simple faint, slower after seizure which may also exhibit Todd's paralysis (*see page 396*)

2. cardiovascular etiologies: Testing is also guided by H&P, vital signs & ECG:

A. cardiac arrhythmia evaluation: 12-lead ECG & 24-hour Holter monitor, and may lead to electrophysiologic (EP) testing/intervention[58, 59]

B. abnormal orthostatics warrants a formal tilt-table test

C. history of cardiomyopathy or CAD merits an echocardiogram and formal stress testing. These results determine the need for cardiac

catheterization

3. neurologic etiologies: comprise < 1% of cases[60]. In the absence of clinical evidence of a neurologic etiology, neurodiagnostic testing (EEG, CT scan, MRI/MRA, carotid doppler) have a diagnostic yield of 2-6%. ∴ These tests are warranted only when clinically indicated[59] (seizures, altered consciousness, gradually resolving Todd's paralysis, known history of cerebrovascular compromise). Tests include:
   A. unenhanced brain CT: rules out most acute neurosurgical etiologies (bleed, hydrocephalus, edema which may be associated with tumor)
   B. MRI without and with enhancement in cases with unexplained CT findings, or with a negative CT but high suspicion of a CNS etiology
   C. seizure evaluation: when symptoms suggest possible seizure:
      1. EEG: usually a sleep deprived EEG. Not very sensitive
      2. 24 hour video EEG monitoring: in cases with high index of suspicion of seizures or nonepileptic seizures

Management: Admission and inpatient management is warranted for patients with diagnosed cardiac or neurologic syncope, either by suggestive history (family history of sudden death, syncope during exertion, witnessed seizure) or diagnostic testing (arrhythmia, severe orthostatic changes, hemodynamic instability)[58, 61].

35.1.15. Transient neurologic deficit

For apoplexy, etc., see *Syncope and apoplexy*, page 1199.

The first three etiologies listed below cover most cases of transient neurologic deficit:

1. **transient ischemic attack (TIA)**: temporary neurologic dysfunction as a result of ischemia. Maximum deficit usually at onset. Most resolve in < 20 mins (*see page 1010*)
2. **migraine**: unlike TIA, tends to progress in a march-like fashion over several minutes. May or may not be followed by headache (see *Migraine*, page 57)
3. **seizure**: may be followed by a Todd's paralysis (*see page 396*)
4. TIA-like syndrome
   A. "tumor TIA": a transient deficit in a patient with a tumor, may be clinically indistinguishable from an ischemic TIA

B. TIA-like symptoms may occur as a prodrome to a lobar intracerebral hemorrhage[62, 63] in cases of cerebral amyloid angiopathy **(CAA)**. Unlike typical TIAs, these usually consist of numbness, tingling or weakness that gradually spreads in a manner reminiscent of a Jacksonian-march and may cross-over vascular territories (*see page 1124*). Caution: antiplatelet drugs and anticoagulation may increase the risk of hemorrhage in patients with CAA (*see page 1122*)

C. chronic subdural hematoma: may cause recurrent TIA-like symptoms of the involved hemisphere[64] (including transient aphasia, hemisensory or motor abnormalities). The duration of symptoms tends to be longer than the typical TIA[64]. Postulated mechanisms include:
   1. electrical basis: the possibility of epileptic activity due has not been supported in the literature; however, spreading depression of Leao has been considered[65]
   2. impairment of venous outflow by compression of surface veins
   3. compromised regional cerebral perfusion by indirect shifting of the anterior and posterior cerebral arteries[66]
   4. transient ICP elevations → variations in cerebral perfusion pressure

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35.1.16. Ataxia/balance difficulties

1. cerebellar origin: usually with involvement of UEs in addition to LEs
   A. cerebellar tumors
   B. cerebellar hemorrhage
   C. acute cerebellar ataxia: usually follows viral infection in a child < 3 years. Usually self-limited with good prognosis for complete recovery
2. spinal cord: usually worse with eyes closed (loss of proprioceptive input)
   A. spinal stenosis
   B. neoplastic cord compression
   C. syringomyelia (may be part of Chiari malformation)
3. degenerative
   A. ataxia-telangiectasia syndrome
   B. ataxia oculomotor apraxia
   C. Friedreich's ataxia
   D. spinocerebellar degeneration

4. metabolic/nutritional
   A. vitamin B12 deficiency
   B. drugs
      1. AEDs (especially phenytoin or carbamazepine)
      2. alcohol: acutely with intoxication and chronic
      3. heavy metal poisoning
5. conditions that may mimic ataxia
   A. weakness
   B. peripheral neuropathy
   C. dizziness: including orthostatic hypotension (see *Dizziness and vertigo*, page 840)
6. peripheral neuropathy:
   A. ataxia can occur with Guillain-Barré syndrome (*see page 66*), especially Miller Fisher variant (*see page 68*)
   B. balance difficulties are common with chronic immune demyelinating polyradiculoneuropathy **(CIDP)** (*see page 68*)

35.1.17. Diplopia

1. cranial nerve palsy of any one or combination of III, IV (rare), or VI
   A. for multiple cranial nerve palsies, see *Multiple cranial nerve palsies (cranial neuropathies)* below
   B. VI palsy: can occur with increased intracranial pressure, e.g. in idiopathic intracranial hypertension (pseudotumor cerebri) (*see page 713*), sphenoid sinusitis… (*see page 836* for other causes of abducens palsy)
   C. isolated muscle paresis of III suggests nuclear lesion or myasthenia gravis
2. intraorbital mass compressing extraocular muscles
   A. orbital pseudotumor: *see page 837*
   B. meningioma
3. Graves' disease: hyperthyroidism + ophthalmopathy (*see page 1219*)
4. myasthenia gravis
5. giant cell arteritis: *see page 74*
6. botulism: due to toxin from *Claustridium botulinum* (in adults: ingested or in wound). N/V, abdominal cramps, and diarrhea often precede neurologic

symptoms. Neurologic involvement is typically symmetric. Dry mouth & cranial nerves palsies (diplopia, ptosis, loss of accommodation and pupillary light reflex) are followed by descending weakness. Bulbar paresis (dysarthria, dysphagia, dysphonia, flaccid facial muscles) follows. Muscles of the trunk/extremities and respiration progressively weaken in a descending fashion. Sensory disturbances are absent. Sensorium usually remains clear

7. following head trauma: includes injury to EOMs, orbital hematoma, VI palsy from increased ICP

35.1.18. Anosmia

1. abrupt onset of anosmia
   A. severe upper respiratory infection with damage to the neuroepithelium: the most common cause
   B. head trauma: second most common cause. Anosmia occurs in 7-15% of patients with significant head trauma
2. gradual onset of anosmia
   A. allergic rhinitis and sinus disease[67]: third most common cause of anosmia (anosmia in this setting may be intermittent)
   B. intracranial neoplasms: olfactory groove meningioma (see *Foster Kennedy syndrome*, page 112), esthesioneuroblastoma (*see page 1230*)
   C. may also be associated with Alzheimer's disease
   D. olfactory sense diminishes with age: ≈ 50% of patients 65-85 years of age have some loss of sense of smell
   E. metabolic abnormalities: vitamin deficiency
   F. physical blockage of nasal passages: nasal polyps…
   G. endocrine abnormalities: diabetes…
   H. chemical: alcohol abuse, exposure to solvents[68], cocaine (ischemic infarction of olfactory mucosa from vasoconstriction)
3. congenital anosmia: Kallmann syndrome (anosmia with hypogonadotrophic hypogonadism[69])

35.1.19. Multiple cranial nerve palsies (cranial neuropathies)

The differential diagnosis is legion. The following is a framework (modified[70]):

1. congenital
   A. **Möbius syndrome**: AKA congenital facial diplegia. Facial plegia is complete in ≈ 35% (in rest, affects upper face more than lower face, unlike central or peripheral facial palsy), associated with abducens palsy in 70%, external ophthalmoplegia in 25%, ptosis in 10%, lingual palsy in 18%
   B. congenital facial diplegia may be part of facioscapulohumeral or myotonic muscular dystrophy
2. infectious
   A. chronic meningitis:
      1. spirochetal, fungal, mycoplasma, viral (including AIDS)
      2. mycobacterial AKA tuberculous **(TB)** meningitis: 6th nerve involved first and most frequently. CSF shows lymphocytic pleocytosis and hypoglycorrhachia. Smears are usually negative and multiple cultures are needed to diagnose
   B. stage II **Lyme disease**: *see page 368*. Facial nerve weakness is common, sometimes bilateral (Lyme disease is the most common cause of facial diplegia in endemic areas). Other cranial nerve involvement is rare
   C. neurosyphilis: rare nowadays except with AIDS. Diagnosed by serologic testing
   D. fungal infection
      1. cryptococcal meningitis: CSF analysis for cryptococcal antigen and India ink prep can detect (*see page 374*)
      2. aspergillosis: may extend to the orbit from sinuses and involve cranial nerves
      3. mucormycosis (phycomycosis): produces cavernous sinus syndrome, usually occurs in diabetics (*see page 836*)
   E. cysticercosis: especially with basal form (see *Neurocysticercosis*, page 370)
3. traumatic: especially with basal skull fractures. Lower cranial nerve palsies may occur (sometimes delayed in onset) with occipital condyle fractures (*see page 954*) or atlanto-occipital dislocation (*see page 952*)
4. neoplastic (brain stem compression and intrinsic lesions usually also produce long tract findings early). Also see *Jugular foramen syndromes*, page 115
   A. chordoma: *see page 676*

B. sphenoid-ridge meningioma
C. neoplasms of the temporal bone (often in conjunction with chronic otitis media and otalgia): adenoid cystic carcinoma, adenocarcinoma, mucoepidermoid carcinoma
D. glomus jugulare tumors: often affects nerves IX, X, and XI. May cause pulsatile tinnitus (see *Paraganglioma*, page 678)
E. carcinomatous or lymphomatous meningitis: CSF pleocytosis and elevated protein. Palsies are painless or associated with diffuse headache. Sensory palsies are common, resulting in deafness and blindness (*see page 711*)
F. invasive pituitary adenomas involving the cavernous sinus (*see page 637*): extraocular cranial neuropathies tend to develop after visual field deficits in these tumors, and are less common when compared to other intracavernous solid tumors[71]
G. primary CNS lymphoma: *see page 672*
H. multiple myeloma involving the skull base: *see page 740*
I. intrinsic brain stem tumors: gliomas, ependymoma, metastases…

5. vascular
   A. aneurysm: intracranial or cavernous sinus (*see page 1056*)
   B. brain stem CVA: usually also produces long tract findings (*see page 114*):
      1. Weber’s syndrome: Cr N III (usually pupil sparing) + contralateral hemiparesis
      2. Millard-Gubler syndrome: Cr N VI + VII + contralateral hemiparesis
   C. vasculitis: Wegener’s granulomatosis usually affects eighth nerve in addition to others
6. granulomatous
   A. sarcoidosis: ≈ 5% have CNS involvement, usually as fluctuating single or multiple cranial neuropathies (facial nerve is most common, and may be indistinguishable from Bell’s palsy). CSF pleocytosis is common (*see page 71*)
7. inflammatory
8. neuropathies
   A. Guillain-Barré syndrome **(GBS)**: cranial nerve involvement includes facial diplegia, oropharyngeal paresis. Peripheral neuropathy usually presents with ascending weakness, proximal muscle weakness > distal,

and absent deep tendon reflexes (*see page 66*)

B. Miller-Fisher variant GBS: ataxia, areflexia & ophthalmoplegia. Serum marker: anti-GQ1b antibodies

C. **idiopathic cranial polyneuropathy**: subacute onset of constant facial pain, usually retro-orbital. Frequently precedes sudden onset of cranial-nerve palsies usually involving III, IV & VI, less frequently V, VII, and lower nerves (IX through XII). Olfactory and auditory nerves usually spared. Acute and chronic inflammation of unknown etiology similar to Tolosa-Hunt and orbital pseudotumor. Steroids reduce pain and expedite recovery

9. entrapment in abnormal bone

   A. **hyperostosis cranialis interna**: a rare autosomal dominant abnormality of the bone of the base of the skull causing recurrent facial palsy and other cranial nerve palsies[72]

   B. osteopetrosis: *see below*

   C. Paget's disease (*see page 498*) involving the skull: 8th nerve involvement (deafness) is most common. Optic nerve atrophy, and palsies of oculomotor, facial, IX, XI, olfactory nerves and others may also occur[73]

   D. fibrous dysplasia: *see page 701*

Facial diplegia

Items culled from the above list that have facial diplegia as a prominent finding:

1. congenital: Möbius syndrome, congenital facial diplegia
2. infectious: Lyme disease
3. neuropathies: Guillain-Barré syndrome
4. isolated 4th ventricle (*see page 309*): compression at the facial colliculus
5. granulomatous: sarcoidosis:

Cavernous sinus syndrome

Multiple cranial nerve palsies (involving any of the cavernous sinus cranial nerves: III, IV, V1, V2, VI) which primarily produce diplopia (due to ophthalmoplegia). Classically the third nerve palsy (e.g. from an enlarging cavernous carotid artery aneurysm) will <u>not</u> produce a dilated pupil because the sympathetics which dilate the pupil are also paralyzed[74 (p 1492)]. Facial pain or altered facial sensation may occur.

For a list of lesions that may produce cavernous sinus syndrome, *see page*

1219.

Osteopetrosis

AKA "marble bone disease" (there may be confusion with the term osteosclerosis; *osteosclerosis fragilis generalisata* is the obsolete term for osteopetrosis). A rare group of genetic disorders of defective osteoclastic resorption of bone resulting in increased bone density, may be transmitted either as autosomal dominant or recessive[75]. The dominant form is usually benign and is seen in adults and adolescents. The recessive ("malignant") form is often associated with consanguinity, and is similar to hyperostosis cranialis interna (*see above*), but in addition to the proclivity for the skull, also involves ribs, clavicles, long bones, and pelvis (long-bone involvement results in destruction of marrow and subsequent anemia). Cranial nerves involved primarily include optic (optic atrophy and blindness are the most common neurologic manifestation), facial, and vestibulo-acoustic (with deafness), trigeminal nerve may also be involved. There may also be extensive intracranial calcifications, hydrocephalus, intracranial hemorrhage and seizures.

Bilateral optic nerve decompression via a supraorbital approach may improve or stabilize vision[75].

35.1.20. Binocular blindness

1. bilateral occipital lobe dysfunction
   A. bilateral posterior cerebral artery flow impairment
      1. top of the basilar syndrome
      2. increased intracranial pressure
         a. hydrocephalus with shunt malfunction
         b. pseudotumor cerebri (idiopathic intracranial hypertension): *see page 713* c. cryptococcal meningitis: decreased visual acuity (*see page 374*)
   B. trauma: bilateral occipital lobe injury (e.g. contrecoup injury)
2. seizures: epileptic blindness
3. migraine: cortical spreading depression
4. posterior ischemic optic neuropathy: usually in the setting of shock
5. bilateral vitreous hemorrhage: e.g. with SAH (Terson's syndrome)
6. functional: conversion reaction, hysterical blindness…

35.1.21. Monocular blindness

Due to a lesion anterior to the optic chiasm.

1. Amaurosis fugax: often described as a “shade coming down” over one eye
   - A. TIA: usually due to occlusion of the retinal artery (*see page 1144*)
   - B. giant cell arteritis (GCA): usually due to ischemia of optic nerve or tracts (less commonly due to retinal artery occlusion)[76] (*see page 75*)
2. trauma: optic nerve injury
3. ruptured carotid cavernous aneurysm: resultant carotid cavernous fistula increases intraocular pressure by impeding venous return
4. intraorbital pathology: tumors
5. injury within the globe: retinal detachment, ocular trauma
6. unilateral vitreous hemorrhage: e.g. with SAH (Terson’s syndrome)

35.1.22. Exophthalmos

Alt. spelling: exophthalmus. Definition: abnormal protrusion of the eyeball. Some authors reserve the term exophthalmos for cases due to endocrinopathies and use proptosis (of the eye) for other causes, but these terms are widely used interchangeably.

Criteria: different criteria are proposed. Anterior displacement of 18 mm (Hertal exophthalmometry can be used to measure clinically - requires intact lateral orbital bone). CT criteria: for most accurate results, the patient’s should have their eyes open and fixated on a point in the primary gaze position. position of equator of the globe (widest part) is distal to a line drawn from lateral orbit to medial canthus, > 2/3 of the globe anterior to this line.

Pulsatile

1. carotid cavernous fistula **(CCF)** (*see page 1113*)
2. transmitted intracranial pulsation due to defect in orbital roof
   - A. seen unilaterally e.g. in neurofibromatosis type 1 (*see page 723*)
   - B. post-op following procedures that remove orbital roof or wall
3. vascular tumors

Non-pulsatile

1. tumor
   A. intraorbital tumor: may be due to mass effect from tumor or to compromised venous drainage from the orbit
      1. optic glioma (*see page 606*)
      2. optic sheath neuroma
      3. lymphoma
      4. optic sheath **meningioma**[77]
      5. orbital involvement with **multiple myeloma**: *see page 740*
      6. orbital invasion by invasive **pituitary adenoma**: *see page 637*
      7. in peds: metastatic neuroblastoma
   B. due to hyperostosis from a sphenoid ridge meningioma
2. Graves' disease (hyperthyroidism + exophthalmos): even though the exophthalmos is usually bilateral with this (80% - *see page 1219*), thyroid disease is still the most common cause of <u>unilateral</u> proptosis[78]
3. enlargement of periorbital fat[79]
4. infection: orbital cellulitis (usually has concomitant sinusitis)
5. inflammatory: orbital **pseudotumor**. Usually unilateral (*see page 837)*
6. hemorrhage
   A. traumatic
   B. spontaneous
7. 3rd nerve palsy: up to 3 mm proptosis from relaxation of the rectus muscles
8. cavernous sinus occlusion (may affect both eyes)
   A. cavernous sinus thrombosis (*see page 1167*)
   B. cavernous sinus tumor obstructing venous outflow
9. pseudo-exophthalmos
   A. congenital macrophthalmos (bull's eye)
   B. lid retraction: e.g. in Graves' disease (*see page 1219*)
   C. coronal craniosynostosis can cause a "relative" proptosis (*see page 230*)

35.1.23. Ptosis

AKA blepharoptosis. Drooping of the upper eyelid.

Distinguished from pseudoptosis (lid droop not resulting from weakness of levator palpebrae superioris **(LPS)**) which can be due to enophthalmos (globe

displaced posteriorly, e.g. with orbital floor blow-out fracture), microphthalmia, blepharospasm, Duane syndrome.

Etiologies of ptosis:

1. congenital: most are simple (autosomal dominant inheritance), complicated ptosis is associated with other findings (e.g. ptosis with ophthalmoplegia)
2. traumatic: injury to eyelid, orbital roof fracture…
3. neurogenic:
   A. third nerve palsy (*see page 834*)
      1. involvement of main trunk of third nerve: can occur intradurally or within cavernous sinus. Ptosis may be an early sign of pituitary tumor expansion (apoplexy) (*see page 635*)
      2. involvement of the superior division of the third nerve within the orbit
   B. Horner's syndrome (*see page 833*): ptosis here is partial (may be a pseudoptosis since weakness is in tarsal muscles, not LPS), and the lower eyelid will higher than the uninvolved contralateral lower eyelid
4. myogenic ptosis
   A. botulinum toxin injection (e.g. Botox®)
   B. myasthenia gravis
5. mechanical ptosis
   A. tumors: neurofibroma, hemangioma, malignant melanoma, mets…
   B. extension of mucocele of frontal sinus
6. pharmacologic (drugs). Partial list:
   A. corticosteroids: including topical
   B. alcohol
   C. opium

35.1.24. Pathologic lid retraction

1. hyperthyroidism: *see page 1219*
2. psychiatric: schizophrenia…
3. steroids
4. Parinaud's syndrome: *see page 114*

35.1.25. Macrocephaly

Macrocephaly means increased size of the head[80]. Although sometimes used synonymously, some contend that the term **macrocrania** by convention refers to a head circumference > 98th percentile[81 (pp 203)]. Also, not to be confused with *macrencephaly* AKA *megalencephaly* (*see below*). In a pediatric practice the 3 most common etiologies in decreasing order of frequency: familial (parents have big heads), benign subdural fluid collections of infancy (*see page 904*), and hydrocephalus.

1. with ventricular enlargement
   - A. (hydrostatic) hydrocephalus **(HCP)** (*see page 311* for etiologies)
     1. communicating
     2. obstructive
   - B. hydranencephaly: *see page 244*
   - C. constitutional ventriculomegaly: ventricular enlargement of no known etiology with normal neurologic function
   - D. hydrocephalus ex vacuo: loss of cerebral tissue (more often associated with <u>micro</u>cephaly, e.g. with TORCH infections)
   - E. vein of Galen aneurysms: *see below*
2. with normal or mildly enlarged ventricles
   - A. "external hydrocephalus": prominent subarachnoid spaces and basal cisterns (see *External hydrocephalus (AKA benign external hydrocephalus)*, page 307)
   - B. subdural fluid
     1. hematoma
     2. hygroma
     3. effusion benign and symptomatic
     4. benign subdural collections of infancy (*see page 904*)
   - C. cerebral edema: some consider this to be a form of pseudotumor cerebri[80]
     1. toxic: e.g. lead encephalopathy (from chronic lead poisoning)
     2. endocrine: hypoparathyroidism, galactosemia, hypophosphatasia, hypervitaminosis A, adrenal insufficiency…
   - D. familial (hereditary) macrocrania: parents also have large heads, the brains eventually "catch up"
   - E. idiopathic
   - F. megalencephaly (AKA macrencephaly): an enlarged brain (*see page*

245)

G. neurocutaneous syndromes: usually due to increased volume of brain tissue (megalencephaly, *see above*)[80]. Seen especially in neurofibromatosis and congenital hypermelanosis (Ito's syndrome). Less common in tuberous sclerosis and Sturge-Weber. Also seen in the rare hemimegalencephaly syndrome

H. arachnoid cyst (AKA subependymal or subarachnoid cyst)[80]: a duplication of the ependyma or arachnoid layer filled with CSF. Usually reach maximal size by 1 month of age and do not enlarge further. Treatment is required in ≈ 30% due to rapid enlargement or growth beyond first month. Cyst may be shunted or fenestrated. Prognosis with true arachnoid cyst is generally good (unlike porencephalic cyst) if no increased ICP or progressive macro-cephaly during 1st year of life

I. arteriovenous malformation: especially vein of Galen "aneurysm" (*see page 1112*). Auscultate for cranial bruit. With vein of Galen aneurysms, macro-cephaly may be due to HCP from obstruction of the sylvian aqueduct[80]. With other malformations, macrocrania may be due to increased pressure in venous system without HCP

J. brain tumors without hydrocephalus: brain tumors are rare in infancy, and most cause obstructive HCP. Tumors that occasionally present without HCP includes astrocytomas. May also be seen in the rare diencephalic syndrome (tumor of anterior hypothalamus, *see page 606*)

K. "gigantism syndromes"
   1. Soto's syndrome: associated with advanced bone age on x-ray, and multiple dysplastic features of face, skin and bones
   2. exomphalomacroglossia-gigantism **(EMG)** syndrome: hypoglycemia (from abnormalities in islets of Langerhans), large birth weight, large umbilicus or umbilical hernia and macroglossia

L. "craniocerebral disproportion"[80] (*see page 904*): may be the same as benign extra-axial fluid of infancy

M. achondroplastic dwarf: cranial structures are enlarged but the skull base is small, giving rise to a prominent forehead and an OFC ≥ 97th percentile for age

N. Canavan's disease: AKA spongy degeneration of the brain, an autosomal recessive disease of infancy prevalent among Ashkenazi Jews. Produces symmetrical low attenuation of hemispheric white

matter on CT[82] and macrocephaly

O. neurometabolic diseases: usually due to deposition of metabolic substances in the brain. Seen in Tay-Sachs gangliosidosis, Krabbe disease…

3. due to thickening of the skull

A. anemia: e.g. thalassemia

B. skull dysplasia: e.g. osteopetrosis (*see page 1204*)

35.1.26. Tinnitus

May be either subjective (heard only by patient) or objective (e.g. cranial bruit, can be heard by examiner as well, usually with a stethoscope). Objective tinnitus is almost always due to vascular turbulence (from increased flow or partial obstruction).

Pulsatile tinnitus

Most cases are due to vascular lesions.

1. pulse synchronous:

A. carotid cavernous fistula (*see page 1113*)

B. AVM:

1. cerebral (pial) AVM
2. dural AVM: *see page 1109*

C. glomus jugulare tumor: *see page 680*

D. cerebral aneurysm: (rare) possibly with turbulent flow in giant aneurysm

E. hypertension

F. hyperthyroidism

G. idiopathic intracranial hypertension (pseudotumor cerebri): *see page 713*

H. transmitted bruit: from heart (e.g. aortic stenosis), carotid artery stenosis (especially external carotid)

I. dehiscent jugular bulb or high riding jugular bulb: normal venous variant

J. rarely with posterior fossa tumors: CP-angle tumors e.g. vestibular schwannoma or meningioma, vascular intraparenchymal tumors e.g. hemangioblastoma (especially in CPA)

K. lesions that can present with a red tympanic membrane
   1. aberrant carotid artery in middle ear
   2. persistent stapedial artery: rare. Arises from aberrant ICA or from junction of horizontal and vertical petrous ICA. Foramen spinosum is absent on the affected side. Enlargement of anterior tympanic segment of seventh nerve canal
   3. glomus tympanicum tumor: *see page 680*

2. non pulse-synchronous: asymmetrical enlargement of sigmoid sinus and jugular vein may produce a low grade hum

Workup for pulsatile tinnitus:

1. MRI without and with enhancement: to look for tumors, e.g. glomus jugulare
2. angiogram: include internal and external carotid injections
3. tests that are usually <u>not</u> helpful and should not be ordered routinely
   A. carotid ultrasound: nonspecific, not sensitive
   B. MRI/MRV: may miss small dural fistulas and do not give details needed for treatment for large ones

Non-pulsatile tinnitus

1. occlusion of external ear: cerumen, foreign body
2. middle ear infection (otitis media)
3. otosclerosis
4. stapedial muscle spasms: as occurs in hemifacial spasm
5. CP-angle tumors: including vestibular schwannoma (*see page 620*)
6. Meniere's disease: *see page 842*
7. labyrinthitis
8. endolymphatic sac tumors: e.g as in von Hippel-Lindau disease (*see page 668*)
9. drugs
   A. salicylates: aspirin, bismuth subsalicylate (Pepto Bismol®)
   B. quinine
   C. aminoglycoside toxicity: streptomycin, tobramicin (tinnitus precedes hearing loss)

35.1.27. Facial sensory changes

1. circumoral paresthesias
   A. hypocalcemia
   B. syringobulbia
2. unilateral facial sensory changes
   A. large vestibular schwannoma
   B. trigeminal nerve neuroma
   C. compression of the spinal trigeminal tract (large compressive lesions may cause bilateral alteration of facial sensation) that chiefly manifests in diminution of pain and temperature sense with little effect on touch sense[83]. The tract usually extends as far down as ≈ C2 (although it may occasionally extend down to C4)

35.1.28. Language disturbance

1. aphasia:
   A. injury to speech areas of brain
      1. Wernicke's aphasia: classically produces fluent aphasia (normal sentence length & intonation, devoid of meaning) (*see page 114*)
      2. Broca's aphasia: faltering, dysarthric (*see page 114*)
      3. conduction aphasia: fluent spontaneous speech and paraphasias, but patients understand spoken or written words, and are aware of their deficit (*see page 114*)
   B. transitory aphasia following a seizure (see *Todd's paralysis*, page 396)
   C. primary progressive aphasia of adulthood: idiopathic & degenerative
2. **akinetic mutism**: seen with bilateral frontal lobe dysfunction (e.g. with bilateral ACA distribution infarction due to vasospasm from a-comm aneurysm rupture or with large bilateral frontal lesions; may actually be abulia) or with bilateral cingulate gyrus lesions
3. muteness of cerebellar origin[84, 85]
4. following transcallosal surgery: as a result of bilateral cingulate gyrus retraction or thalamic injury together with section of the midportion of the corpus callosum[86]

35.1.29. Swallowing difficulties

1. mechanical: the term globus describes a sensation of a lump in the throat

    A. ossification of the anterior longitudinal ligament (OALL): *see page 506*
        1. as part of diffuse idiopathic skeletal hyperostosis (DISH): *see page 506*
    B. post-op following ACDF
        1. it is normal to have a little swelling and fullness early post-op
        2. may be increased with multiple levels and with anterior plating
        3. as a complication from post-op hematoma
2. neurologic

35.2. Differential diagnosis (DDx) by location

35.2.1. Posterior fossa lesions

35.2.1.1. Cerebellar lesions

The following addresses intra-axial p-fossa abnormalities (for extra-axial lesions, see *Cerebellopontine angle (CPA) lesions* below).

ADULT

Single lesion

Rule of thumb: "the differential diagnosis of a solitary intraparenchymal lesion in an adult p-fossa is metastasis, metastasis, metastasis, until proven otherwise".

1. tumors:
    A. metastasis
    B. **hemangioblastoma**: (*see page 667*) the most common PRIMARY intra-axial p-fossa tumor in adults (7-12% of p-fossa tumors). Very vascular nodule, often has cyst. Almost all p-fossa tumors are relatively avascular on angiography except these (look for serpentine signal voids especially in the periphery of the lesion on MRI[87], much less common in cavernous hemangioma)
    C. pilocytic astrocytoma: solid or cystic, tends to occur in younger adults

(*see page 604*)

D. brainstem glioma: an isolated glioblastoma in the posterior fossa of an adult is a reportable rarity

E. choroid plexus tumor: usually infratentorial in adults (*see page 695*)

F. cerebellar liponeurocytoma: *see page 613*

2. infectious: abscess
3. vascular
   A. cavernous hemangioma
   B. hemorrhage
   C. infarction: cerebellar CVA may be associated with H/A and/or pain in sub-occipital region or upper neck
      1. embolic
      2. thrombotic/plaque related
      3. vertebral artery dissection: much less common than carotid dissection (*see page 1163*)
      4. vertebrobasilar hypoplasia: *see page 1160*
4. Lhermitte-Duclos: *see page 593*. Focal or diffuse. Nonenhancing. Characteristic tiger stripes. Widens folia (c.f. most neoplasms which destroy folial pattern)

Multiple lesions

1. metastases
2. hemangioblastoma (possibly as part of von Hippel-Lindau): *see page 667*
3. abscesses
4. cavernous hemangiomas

PEDIATRIC

Also see *Pediatric brain tumors*, page 697.

Currently: p-fossa tumors comprise 54-60% of childhood brain tumors (breakdown listed below). 4 types account for ≈ 95% of infratentorial tumors in patients ≤ 18 yrs age[88]. The 3 most common are equal in incidence[81]:

1. PNET (including **medulloblastoma**): 27% (*see page 686*)
   A. most start in <u>roof</u> of 4th ventricle (fastigium), and most are solid
   B. differentiating medulloblastoma **(MB)** from ependymoma:
      1. 4th ventricle drapes around medulloblastoma ("**banana sign**") from the anterior aspect, c.f. ependymoma which tends to grow

into 4th ventricle from floor. Ependymoma may grow through foramen of Luschka and/or Magendie
   2. ependymomas tend to be inhomogeneous on T1WI MRI (unlike MB)
   3. the exophytic component of ependymomas tends to be high signal on T2WI MRI (with MB this is only mildly hyperintense)
   4. calcifications: common in ependymomas, but only in < 10% of MB
2. **cerebellar (pilocytic) astrocytoma**: 27%. Most start in cerebellar hemisphere. Often cystic with enhancing mural nodule (*see page 604*)
3. **brainstem gliomas**: 28%. Usually present with multiple cranial nerve palsies and long tract findings (*see page 607*)
4. ependymoma: usually arise in <u>floor</u> of 4th ventricle (*see page 683*)
5. choroid plexus papilloma: majority of patients are < 2 yrs old (*see page 695*)
6. atypical teratoid/rhabdoid tumor **(AT/RT)**: *see page 688*
7. metastasis: neuroblastoma, rhabdomyosarcoma, Wilm's tumor…
8. PHACES syndrome: acronym for a group of findings including Posterior fossa malformations, cervicofacial Hemangioma, Arterial anomalies of the head and neck, Coarctation of the aorta and cardiac defects, Eye anomalies and Sternal cleft. Ratio girls:boys = 9:1. Thought to begin during gestation weeks 8-10

35.2.1.2. Cerebellopontine angle (CPA) lesions

Vestibular schwannoma, meningioma, and epidermoid account for most. For those lesions that may be cystic, *see below*.

1. **vestibular schwannoma**: 80-90% of CPA lesions } *see below* to differentiate these two lesions
2. **meningioma**: (5-10%) } *see below* to differentiate these two lesions
3. ectodermal inclusion tumors (*see page 688*)
   A. **epidermoid** (cholesteatoma): 5-7%. High signal on DWMRI (*see page 689*). Tumor passing from the posterior fossa to the middle fossa though the incisura is highly suggestive of epidermoid
   B. dermoid
4. metastases
5. neuroma from cranial nerves other than VIII (also *see below*)
   A. trigeminal neuroma: expands towards Meckel's cave

B. facial nerve neuroma[89]: may arise in any portion of the VII nerve, with a predilection for the geniculate ganglion[90]. Hearing loss may be sensorineural from VIII nerve compression from tumors arising in the proximal portion of VII (cisternal or internal auditory canal **(IAC)** segment), or it may be conductive from erosion of the ossicles by tumors arising in the second (tympanic, or horizontal) segment of VII. Facial palsy (peripheral) may also develop, usually late[89] (*see page 845*)

C. neurinoma of lowest 4 cranial nerves (IX, X, XI, XII)

6. arachnoid cyst: *see page 222*
7. neurenteric cyst: rare[91] (*see page 227*). May secrete mucin
8. cholesterol granuloma (distinct from epidermoid): *see page 689*
9. lipoma
10. aneurysm: PICA, AICA, vertebrobasilar
11. dolichobasilar ectasia
12. cysticercosis
13. extensions of:
    A. brain stem or cerebellar glioma
    B. pituitary adenoma
    C. craniopharyngioma
    D. chordoma & tumors of skull base
    E. fourth ventricle tumors (ependymoma, medulloblastoma)
    F. choroid plexus papilloma: from 4th ventricle through foramen of Luschka
    G. glomus tumor
        1. glomus jugulare
        2. glomus tympanicum
    H. primary tumors of temporal bone (e.g. sarcoma or carcinoma)

Cystic lesions of the CPA

CPA lesions from the above list that may be cystic or have a cystic component[91]:

1. arachnoid cyst: same intensity as CSF on all MRI sequences, homogeneous
2. epidermoid cyst: ★ high signal on DWMRI differentiates this from arachnoid cyst (*see page 690*)
3. dermoid cyst: high intensity areas on T1WI similar to fat; usually midline

4. cystic schwannoma
5. cholesterol granuloma: ★ ≈ only lesion that is high signal on T1WI[A] (due to blood breakdown products). Also high signal on T2WI. Usually extradural, especially near petrous apex. Bone destruction is common
6. neurenteric cyst: nonenhancing. Low intensity on DWMRI
7. choroidal cyst
8. cysticercosis: enhancing nodule (scolex)

A. exception: the rare “white” epidermoid

Differentiating neuromas of V, VII and VIII cranial nerves

All 3 may present in the CPA and may cross from posterior fossa to middle fossa, but they do so in different manners. Vestibular schwannomas show “transhiatal” extension by passing through the tentorial hiatus medially. Most trigeminal neuromas show “transapicopetrosal” extension by crossing into the middle fossa via the petrous apex (although some show transhiatal extension). When facial neuromas cross, they tend to spread across the midpetrosal bone, which is characteristic for facial neuromas[89]. When a facial neuroma enlarges the IAC, unlike a vestibular schwannoma, it tends to erode the anterosuperior aspect of the IAC.

Differentiating vestibular schwannoma from CPA meningioma

- vestibular schwannoma **(VS)** (AKA acoustic neuroma):
  A. clinical: progressive unilateral hearing loss, usually with tinnitus. Progression results in unsteadiness, with true vertigo being rare. The facial nerve is more resistant to stretching, thus facial nerve signs and symptoms occur late. Trigeminal nerve involvement may occur with tumors > 3 cm (check corneal reflex), with tic douloureux-like symptoms being unusual
  B. imaging: often heterogeneous signal and nonuniform enhancement. Rarely calcified. Except for very small tumors, IAC is frequently enlarged. Look for an acute angle between the tumor and the petrous

bone, (meningiomas usually have an obtuse angle)

- meningiomas: may mimic VSs with these differences:
  - A. clinical: since they often arise from the superior anterior edge of the IAC, early facial nerve involvement is more common, and hearing loss is usually late. Trigeminal neuralgia-like pain is more common than with VSs
  - B. imaging: homogeneous signal and enhancement. IAC usually not enlarged. Calcification, and bony hypertrophy may occur (which occasionally narrows the IAC)

35.2.1.3. Petrous apex lesions

1. infection/inflammatory:
   - A. osteomyelitis: may produce Gradenigo's syndrome (*see page 838*)
   - B. cholesterol granuloma (bright on T1WI epidermoid cyst are bright on DWI, neither enhance)
2. vascular lesions: aneurysm
3. neoplastic:
   - A. squamous cell cancer
   - B. glomus tumor
   - C. chondrosarcoma: will displace the carotid from medial to lateral (almost every other tumor in this region encases the carotid)

35.2.1.4. Foramen magnum lesions

1. extra-axial tumors: for more details of tumors (i.e. neoplasms only) *see page 711*
   - A. meningioma
   - B. chordoma: a mass behind the dens compressing the spinal cord is a chordoma until proven otherwise (*see page 675*)
   - C. neurilemmoma
   - D. epidermoid
   - E. chondroma
   - F. chondrosarcoma
   - G. metastases
2. non-neoplastic
   - A. aneurysms or ectasia of the vertebral artery

B. odontoid process in cases of basilar invagination (*see page 138*)
C. pannus from involvement of the odontoid with rheumatoid arthritis or old nonunion of fracture
D. synovial cyst of the quadrate ligament of the odontoid[92]

35.2.2. Multiple intracranial lesions on CT or MRI

1. neoplastic
   A. primary
      1. multicentric gliomas (≈ 6% of gliomas are multicentric, more common in neurofibromatosis, see *Multiple gliomas*, page 597)
      2. tuberous sclerosis (including giant cell astrocytomas); (usually periventricular)
      3. multiple meningiomas
      4. lymphoma
      5. PNET
      6. multiple neuromas (usually in neurofibromatosis, including bilateral vestibular schwannomas)
   B. metastatic: usually cortical or subcortical, surrounded by prominent vasogenic edema. *See page 702*. More common tumors include:
      1. lung
      2. breast
      3. melanoma: may be higher density than brain on unenhanced CT
      4. renal cell
      5. gastrointestinal tumors
      6. genitourinary tract tumors
      7. choriocarcinoma
      8. testicular
      9. atrial myxoma
      10. leukemia
2. infection: mostly abscess or cerebritis. Most commonly due to:
   A. pyogenic bacteria
   B. toxoplasmosis: common in AIDS patients (*see page 364*)
   C. fungal
      1. cryptococcus
      2. mycoplasma
      3. coccidiomycosis

        4. aspergillosis
        5. candidiasis
    D. echinococcus
    E. schistosomiasis
    F. paragonimiasis
    G. herpes simplex encephalitis **(HSE)**: usually temporal lobe (*see page 358*)
3. inflammatory
    A. demyelinating disease
        1. MS: usually in white matter, periventricular, with little mass effect, margins are usually very sharp. Ring enhancing lesions can occur with tumefactive demyelinating lesions (*see page 64*)
        2. progressive multifocal leukoencephalopathy **(PML)**: primarily in white matter. No enhancement. Patients are usually very sick
    B. gummas
    C. granulomas
    D. amyloidosis
    E. sarcoidosis
    F. vasculitis or arteritis
    G. collagen vascular disease, including:
        1. periarteritis nodosa **(PAN)** (*see page 77*)
        2. systemic lupus erythematosus **(SLE)**
        3. granulomatous arteritis
4. vascular
    A. multiple aneurysms (congenital or atherosclerotic)
    B. multiple hemorrhages, e.g. associated with DIC or other coagulopathies (including anticoagulant therapy)
    C. venous infarctions (especially in dural sinus thrombosis, *see page 1166*)
    D. moyamoya disease (*see page 1170*)
    E. subacute hypertension (as in malignant HTN, eclampsia…) → symmetric confluent lesions with mild mass effect and patchy enhancement usually in occipital subcortical white matter (*see page 73*)
    F. multiple strokes
        1. lacunar strokes (l'etat lacunaire)
        2. multiple emboli (e.g. in atrial fibrillation, mitral valve prolapse,

SBE, air emboli)
3. sickle cell disease
4. vasculitis
5. intravascular lymphomatosis: *see page 674*

5. hematomas and contusions
   A. traumatic (multiple hemorrhagic contusions, multiple SDH)
   B. multiple “hypertensive” hemorrhages (amyloid angiopathy, etc.)
6. intracranial calcifications (*see page 1223*)
7. miscellaneous
   A. radiation necrosis
   B. foreign bodies (e.g. post gunshot wound)
   C. periventricular low densities
      1. Binswanger’s disease
      2. transependymal absorption of CSF (e.g. in active hydrocephalus)

Evaluation

Deciding which of the following tests are needed to evaluate a patient with multiple intracranial lesions must be individualized for the appropriate clinical setting.

1. cardiac echo: to R/O SBE that could shed septic emboli
2. “metastatic workup” (see *Metastatic work-up*, page 706) including:
   A. chest x-ray: to R/O primary bronchogenic Ca or pulmonary metastases of another Ca, but also to R/O pulmonary abscess that could shed septic emboli. Chest CT may be needed in cases of positive CXR or if CXR is negative and there is high suspicion of lungs as source of primary
   B. abdominal CT: has largely replaced lower GI (barium enema) and IVP
   C. mammogram in women

35.2.3. Ring-enhancing lesions on CT/MRI

Abscess vs. tumor: (*see Figure 35-1* and *Figure 35-2*) Tumor: the enhancing ring may be incomplete and irregular. Abscess: ring is usually complete, often thinner and smoother than with tumor. Abscess: usually brighter than tumor on DWI MRI.

Multiple lesions: metastases or abscess are much more likely than astrocytoma.

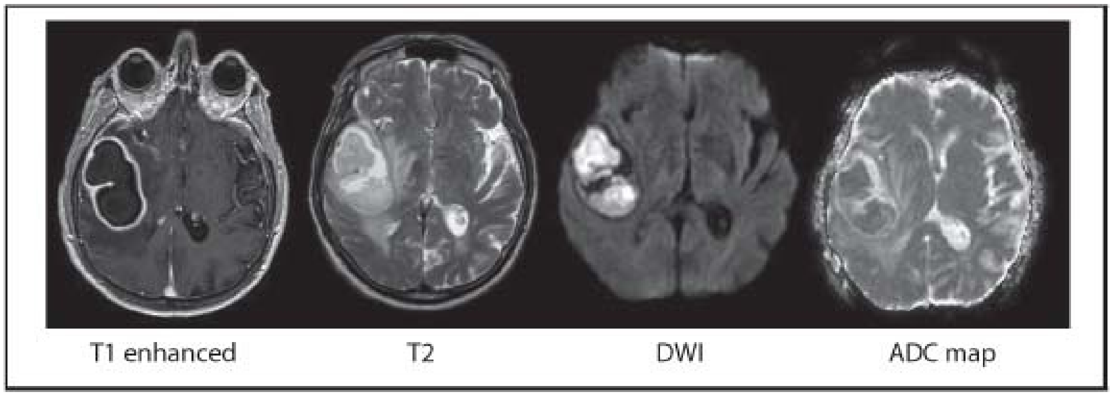

Figure 35-1 MRI of right hemispheric cerebral abscess (bright on DWI)

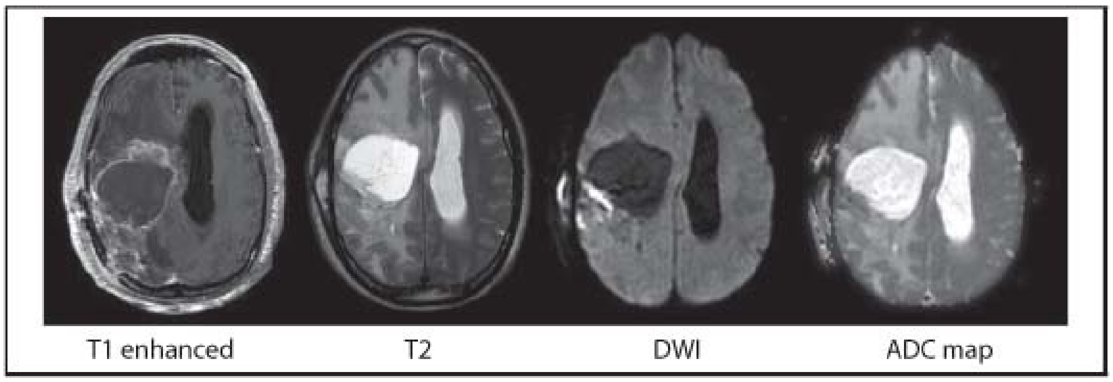

Figure 35-2 MRI of right hemispheric glioblastoma (dark on DWI)

Bold entries account for most cases in adults. Also consider lymphoma.

1. **astrocytoma**: usually malignant astrocytoma, viz. glioblastoma multiforme
2. **metastases**: (*see page 702*) especially lung
3. **abscess**: *see page 350*
   A. may see visible growth over several days on serial imaging
   B. pyogenic abscesses are often (but not always) associated with fever and rapidly progressing neurologic deficit
   C. *Nocardia* abscesses are often multiloculated (*see page 356*) and are usually associated with a lung lesion
4. others
   A. lymphoma (primary brain lymphoma or metastatic systemic lymphoma): wall is thicker than abscess[93]. Incidence is increasing (*see page 672*)
   B. radiation necrosis
   C. resolving intracerebral hematoma: on T1 gradient echo sequence, a

continuous ring suggests hematoma, an interrupted ring suggests malignancy

D. cystic lesions with enhancing wall:
   1. cysticercosis cyst (see *Neurocysticercosis*, page 370)

E. trauma

F. recent infarct

G. thrombosed giant aneurysm

35.2.4. White matter lesions

LEUKOENCEPHALOPATHY

Disease largely confined to the white matter. Demyelinating disease cause most.

Appear as white matter low density on CT or low signal on T1WI MRI, and high-intensity on T2WI. Usually does not enhance. Unlike a CVA, changes tend to spare the cortex. Conditions such as metabolic derangements, leuko-araiosis, etc. tend to produce fairly symmetric findings.

Differential diagnosis:

1. anoxia/ischemia
2. demyelinating disease
   A. MS
   B. ADEM
3. intoxication: cyanide, organic solvents, carbon monoxide
4. vitamin deficiencies: B_{12} with subacute combined degeneration
5. infectious, especially viral:
   A. progressive multifocal leukoencephalopathy **(PML)** (*see page 364*)
   B. herpes varicella-zoster leukoencephalitis (*see page 360*)
   C. HIV infection (AIDS): perivascular pattern of demyelination
   D. cytomegalovirus infection
   E. Creutzfeldt-Jakob disease: small and perivascular demyelination
6. metabolic derangements: hyponatremia, excessively rapid correction of hyponatremia (causing osmotic myelinolysis, *see page 11*)
7. hereditary: metachromatic leukodystrophy, adult-onset Schilder's disease
8. leuko-araiosis (*see page 1227*)
9. multiple myeloma (*see page 740*)

10. low grade (WHO grade II infiltrating) glioma (*see page 595*)

35.2.5. Corpus callosum lesions

1. lymphoma
2. MS plaque
3. tumefactive demyelinating lesions: *see page 64*
4. lipoma

35.2.6. Sellar, suprasellar and parasellar lesions

May enlarge, erode or destroy the sella turcica. Considerations in adults (adenoma is the most common enhancing pituitary lesion) are different than for children (adenomas are rare, craniopharyngioma and germinoma are more common). Includes (modified[94]):

1. tumors/pseudotumors
    - A. tumors having epicenter within the sella
        1. pituitary tumor
            - a. adenohypophyseal tumors
                - i. adenoma
                    1. microadenoma: < 1 cm diameter (*see page 634*)
                    2. macroadenoma: ≥ 1 cm diameter
                    3. invasive adenoma: *see page 637*. Includes aggressive tumors of Nelson's syndrome (*see page 639*)
                - ii. pituitary carcinoma or carcinosarcoma: *see page 634*
            - b. neurohypophyseal tumors
                - i. metastases: the most common tumor found in the posterior pituitary (presumably due to rich blood supply): breast and lung are most common primaries[95]
                - ii. pituicytoma: the most common tumor arising from neurohypophysis/pituitary stalk (i.e. primary) (*see page 641*)
                - iii. astrocytoma: arising from stalk or posterior pituitary
        2. pituitary "pseudotumor":
            - a. hyperplasia (enlargement)
                - i. thyrotroph hyperplasia due to primary hypothyroidism[96] causing chronic pituitary stimulation by TRH *see page 645*. Typically: free T_4 low or normal, TSH ↑↑, symmetrical sellar

mass on MRI
ii. gonadotroph hyperplasia: due to primary hypogonadism
iii. somatotroph hyperplasia: due to ectopic GH-RH secretion
iv. lactotroph hyperplasia: in pregnancy
b. pituitary enlargement may occur in intracranial hypotension (*see page 305*)
c. the pituitary gland of young women of childbearing potential is normally slightly enlarged

B. juxtasellar or suprasellar tumors or masses: any of these lesions may extend into the sella

1. craniopharyngioma: in this region, these account for 20% of tumors in adult, 54% in peds (*see page 663*)
2. Rathke cleft cyst: *see page 665*
3. meningioma (parasellar, tuberculum sellae, or diaphragma sellae): to differentiate tuber-culum sellae meningioma from pituitary macroadenoma on MRI (*see Figure 35-3*), 3 characteristics of meningioma are: 1) bright homogeneous enhancement with gadolinium (c.f. heterogeneous, poor enhancement with macroadenoma), 2) suprasellar epicenter (vs. sellar), 3) tapered extension of intracranial dural base[97] (dural tail). Also, the sella is usually not enlarged, and even large suprasellar meningiomas rarely produce endocrine disturbances[98]. The pituitary stalk is sometimes seen being pushed posteriorly by a meningioma. Tuberculum sellae meningiomas may be associated with sphenoid pneumosinus dilatans[99] (enlargement of the underlying sphenoid sinus without bone erosion)
4. pituitary tumor (mostly adenomas) with extrasellar extension: tends to push carotids laterally (unlike meningioma which may encase carotid), more symmetric than meningioma
5. germ cell tumors **(GCT)**: (*see page 692*) choriocarcinoma, germinoma, teratoma, embryonal carcinoma, endodermal sinus tumor. In females, suprasellar GCTs are more common; in males pineal region is more common
   a. suprasellar GCT: triad of diabetes insipidus, visual deficit and panhypopituitarism[100]. May also present with obstructive hydrocephalus
   b. simultaneous suprasellar and pineal lesions is diagnostic of GCT (so-called synchronous germ cell tumors - *see page 692*)

6. glioma
   a. hypothalamic glioma
   b. optic nerve or chiasm (optic glioma): *see page 606*
7. metastasis
8. chordoma
9. parasitic infections: cysticercosis
10. epidermoid cyst
11. suprasellar arachnoid cyst: see *Arachnoid cysts*, page 222
12. sarcoidosis: (*see page 71*) hypothalamic involvement is a more likely site as a cause of anterior and/or posterior pituitary insufficiency
13. bone abnormalities
   a. giant cell tumor: *see page 742*
   b. chondromyxoid fibroma
   c. brown tumor of hyperparathyroidism
   d. bone spur
   e. extramedullary hematopoiesis[101]

2. vascular lesions
   A. aneurysm: ACoA, ICA (cavernous carotid or suprasellar variant of superior hypophyseal artery aneurysm, *see page 1070*), ophthalmic, basilar bifurcation. Giant aneurysms may produce mass effect
   B. carotid cavernous fistula (CCF): *see page 1113*
3. inflammatory:
   A. (autoimmune) **hypophysitis** (*see below*):

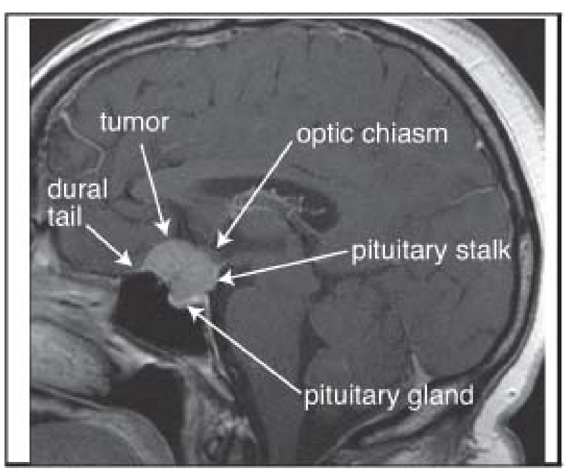

Figure 35-3 Tuberculum sellae meningioma that could be mistaken for a pituitary adenoma. Contrast enhanced T1WI sagittal MRI

1. distinguishing imaging characteristics are shown in *Table 35-5*
2. the most important *clinical* feature: pregnancy
3. the most important laboratory feature: diabetes insipidus (if DI is present, it is unlikely to be an adenoma)

B. pituitary granuloma[102]

4. empty sella syndrome:
   A. primary: *see page 719*
   B. secondary: following pituitary tumor resection (*see page 719*)

Table 35-5 Imaging characteristics of hypophysitis vs. adenoma[103]

Feature	Hypophysitis	Adenoma
Enlargement	symmetric	asymmetric
Pituitary stalk	thickened, nontapering	not thickened, -tapering, deviated
Sellar floor*	spared	may be eroded
Enhancement	intense, may be heterogeneous	less intense, usually homogeneous
Mean size at time of presentation	3 cm^3	10 cm^3
Posterior pituitary bright spot†	lost	preserved in 97%

* on CT scan

† the normal hyperintensity of the posterior pituitary on T1WI MRI[104] (*see page 648*)

HYPOPHYSITIS

AKA autoimmune hypophysitis **(AH)** Two main forms:

1. **lymphocytic (adeno)hypophysitis** 103: the more commonly encountered form. Inflammation of the pituitary stalk with lymphocytic infiltrate. Well established autoimmune etiology, although the antigens have not been identified. Primarily affects women in late pregnancy or early postpartum period
2. **granulomatous hypophysitis**: more aggressive. No gender bias. No association with pregnancy. May be autoimmune, but pathogenesis not definitely known

Because AH often mimics a nonsecretory pituitary macroadenoma (enhancing sellar mass on imaging, with negative endocrine tests), these lesions often undergo surgical resection instead of what may be more appropriate medical therapy (e.g. steroids[105], or discontinuing possible offending agents such

as ipilimumab[106]).

For distinguishing imaging characteristics, *see Table 35-5*.

35.2.7. Intracranial cysts

Modified[107]:

1. arachnoid cysts: *see page 222*. Typically lined with meningothelial cells
2. suprasellar cyst from dilated third ventricle
3. interhemispheric cyst from porencephaly
4. neuroectodermal cysts (glioependymal cysts): intraparenchymal, located near ventricles
5. old infarct: if it communicates with ventricle it is called a porencephalic cyst
6. tumor cysts (the solid portion may sometimes be isodense to brain on CT):
   A. ganglioglioma: usually solid but may appear cystic on CT (*see page 677*)
   B. pilocytic astrocytoma (*see page 603*): usually has enhancing mural nodule
   C. neurilemmomas may be cystic
   D. supratentorial ependymomas are often cystic: *see page 683*
7. infectious
   A. abscess
   B. cysticercosis: see *Neurocysticercosis*, page 370
   C. hydatid cyst: see *Echinococcosis*, page 373
8. pineal cysts: *see page 691*
9. colloid cyst: *see page 665*
10. Rathke's cleft cyst: *see page 665*
11. giant aneurysm
12. on CT, a low density non-enhancing tumor can mimic a cyst
13. chronic subdural hematoma or hygroma may mimic a cyst
14. **posterior fossa**: (for cysts of the CPA *see page 1211*). Includes:
    A. cyst associated with Dandy-Walker malformation (*see page 240*)
    B. epidermoid: *see page 689*
    C. enlarged cisterna magna may mimic a cyst
    D. cerebellar hemangioblastoma: often has an enhancing mural nodule

(*see page 667*)

E. arachnoid cyst of posterior fossa

F. neurenteric cyst: *see page 227*

G. pilocytic astrocytoma of the cerebellum (*see page 604*): usually has an enhancing mural nodule

MIDLINE CAVITIES

Three potential supratentorial midline cavities in the center of the brain and differentiating features are shown in *Table 35-6*.

Table 35-6 Features of midline brain cavities[108]

Cavity	Anatomy	Frequency	Clinical significance
cavum septum pellucidum **(CSP)** *(see text)*	located between leaflets of septum pellucidum	100% of preemies, 97% of newborns, 10% of adults	no known association with pathologic conditions
cavum vergae	directly posterior to, and often communicating with CSP	relatively uncommon	possible association with neurologic abnormalities*
cavum velum interpositum	due to separation of crura of fornix between thalami above the 3rd ventricle	present in 60% of children < 1 yr age, and in 30% between 1 and 10 yrs	no known association with pathologic conditions

* including developmental delay, macrocephaly, Apert's syndrome, abnormal EEG

Cavum septum pellucidum (CSP)

AKA fifth ventricle, among others. A variable slit-like fluid-filled space between the leaflets of the left and right septum pellucidum. The compartment is usually isolated, although some communicate with third ventricle. The CSP is part of normal development, and persists until shortly after birth. Thus, it is present in ≈ all preemies. It is found in ≈ 10% of the adult population, usually representing an asymptomatic developmental anomaly. However, it is also commonly seen in boxers suffering from chronic traumatic encephalopathy (*see page 911*).

35.2.8. Orbital lesions

4 compartments of the orbit: 1) ocular (AKA globe, AKA bulbar), 2) optic nerve sheath, 3) intraconal, and 4) extraconal. CT remains a strong imaging modality within the orbit (less susceptible to motion artifact than MRI, images bony structures to good advantage). For pediatrics, *see below*.

Orbital lesions in adults: Orbital pseudotumor is the most common.

1. neoplastic

A. cavernous hemangioma: the most common benign primary intra-orbital neoplasm. Choroidal hemangioma is seen in Sturge-Weber syndrome } discrete tumors that may occur adjacent to but not envelope the optic nerve sheath
B. fibrohistiocytoma } discrete tumors that may occur adjacent to but not envelope the optic nerve sheath
C. hemangiopericytoma } discrete tumors that may occur adjacent to but not envelope the optic nerve sheath
D. capillary hemangioma: produces infantile proptosis. Regresses spontaneously
E. lymphangioma: produces infantile proptosis. Does not regress
F. melanoma: the most common primary ocular malignancy of adulthood
G. retinoblastoma: congenital, malignant primary retinal tumor. 40% are bilateral, 90% are calcified (often a key differentiating feature; does not portend benignity as with other lesions). CT may show retinal detachment
H. lymphoma of the orbit: causes painless proptosis. The 3rd most common cause of proptosis
I. intraorbital meningioma
J. primary optic nerve tumors
    1. optic glioma
    2. optic nerve sheath tumor (schwannoma)

2. congenital
    A. Coats disease: telangiectatic vascular malformation of retina which leaks a lipid exudate causing retinal detachment. May mimic retinoblastoma. Vitreous is hyperintense on MRI on both T1WI and T2WI due to lipid
    B. persistent hyperplastic primary vitreous
    C. retinopathy of prematurity (retrolental fibroplasia)
3. infectious
    A. toxocara endophthalmitis
4. inflammatory/collagen vascular disease: usually bilateral
    A. scleritis
    B. pseudotumor of the orbit: the most common intraconal lesion. Usually uni-lateral (*see page 837*)
    C. sarcoidosis: usually affects the conjunctiva and lacrimal gland and spares connective tissues and intraorbital muscles

    D. Sjögren's syndrome
5. vascular
    A. enlargement of the superior orbital vein: may occur in thrombosis of cavernous sinus or in carotid-cavernous fistula
    B. dural AVM
6. miscellaneous
    A. drusen: degenerated retinal pigment cells in the posterior globe that may resemble calcified masses on CT
    B. thyroid ophthalmopathy: Graves' disease (hyperthyroidism & swelling of EOMs → painless proptosis). 80% of cases are bilateral. The ophthalmopathy is independent of the level of thyroid hormone (possibly an autoimmune process). NB: a swollen inferior rectus muscle may resemble an orbital tumor if seen only on lower CT cut through the orbit
    C. EOM enlargement with steroid use or occasionally with obesity
    D. fibrous dysplasia

Orbital tumors in pediatrics:

1. dermoid cyst: 37%. The most common lesion in children
2. hemangioma: 12%. Most regress spontaneously without surgery
3. rhabdomyosarcoma: 9%. The most common malignant tumor of the orbit
4. optic nerve glioma: 6%
5. lymphangioma: < 7%. Imaging resembles hemangioma. But will not regress spontaneously, requires surgery. Proptosis may worsen after a URI. May bleed into itself (chocolate cysts)

35.2.9. Cavernous sinus lesions

Modified[109]:

1. primary tumors (rare)
    A. meningiomas[110]
    B. neurinomas
2. tumors from adjacent areas that may extend into cavernous sinus (head and neck cancers may track intracranially along cranial nerves, especially V):
    A. meningiomas

B. neurinomas
C. chordomas
D. chondromas
E. chondrosarcomas
F. pituitary tumors[111]
G. nasopharyngeal carcinomas
H. esthesioneuroblastomas
I. nasopharyngeal angiofibromas
J. metastatic tumors

3. inflammation: e.g. Tolosa-Hunt (*see page 837*)
4. infection: mucormycosis (phycomycosis). Usually in diabetics (*see page 836*)
5. vascular
   A. cavernous carotid aneurysm
   B. carotid-cavernous fistula (*see page 1113*)
   C. cavernous sinus thrombosis

35.2.10. Skull lesions

The most common benign tumors of skull are osteoma and hemangioma. Osteogenic sarcoma is the most common malignancy. *See page 698* for specific skull tumors.

EVALUATING ROENTGENOGRAPHIC SKULL LUCENCIES

There is enough overlap of features to prevent any systematic means of determining the etiology of all or even most radiographic skull lucencies. The following features should be noted for any lucency, some are more helpful than others (modified[112]):

1. multiplicity (single or multiple?): except for multiple venous lakes, the presence of 6 or more defects is usually indicative of a malignancy
2. origin (intradiploic, full thickness, inner or outer table only):
   A. most vault lesions originate intradiploically, so limitation to this space may merely signify early recognition of a lesion
   B. expansion of the diploë with bulging of one or both tables almost always signifies a benign lesion
   C. full thickness lesions affecting both tables congruently usually

indicates malignancy, whereas non-congruent erosion is more common with benign lesions

3. edges (smooth or ragged):
   A. smooth edges, whether regular, distinct or indistinct: no predictive value
   B. irregular margins (especially ragged undermined edges): more suggestive of infection (osteomyelitis) or malignancy
   C. sharply demarcated, full thickness punched out defects: suggest myeloma
4. presence of peripheral **sclerosis**: circumferential bony sclerosis suggests benignity (may indicate slow expansion and longstanding nature). The ring of sclerosis is generally narrow except in fibrous dysplasia
5. presence or absence of peripheral vascular channels: presence is highly suggestive of benign lesions (seen in ≈ 66% of venous lakes and ≈ 50% of hemangiomas)
6. pattern within the lucency:
   A. ★ hemangiomas classically show <u>honeycomb</u> or <u>trabecular</u> pattern (seen in ≈ 50% of cases) or <u>sunburst</u> pattern (seen in ≈ 11% of cases)
   B. fibrous dysplasia may show well defined islands of bone, or a grossly mottled appearance with randomly arranged cystic and dense areas
7. location on the cranial vault (high vs. low): poor correlation with benign vs. malignant lesions
8. pain: eosinophilic granulomas are often <u>tender</u>

Remember: skull lesions may have an intracranial component. CT scanning is good for assessing bone (MRI is poor for this), however, CT may miss small intracranial lesions tucked within the convexity of the calvaria due to bone hardening artifact (MRI has better sensitivity in this setting).

Nuclear bone scan may be a helpful adjunctive test (see specific lesion for findings).

Biopsy: indicated for questionable skull lesions. If the bone has not been destroyed by soft tissue, biopsy may be accomplished with a Craig needle, and the specimen may need decalcification by the pathologist before histologic evaluation can be completed.

RADIOLUCENT LESION OR BONE DEFECT IN SKULL (AKA LYTIC LESIONS)

- congenital or developmental
  A. epidermoid (cholesteatoma): <u>sclerotic</u> edge

B. congenital: encephalocele, meningoencephalocele, dermal sinus

C. **fibrous dysplasia**: *see page 701*. A benign condition in which normal bone is replaced by fibrous connective tissue. Tends to occur higher in calvaria. 3 types:

1. cystic: widening of the diplöe usually with thinning of the outer table and little involvement of the inner table. Typically involves calvaria
2. sclerotic: usually involves skull base (especially sphenoid bone) and facial bones
3. mixed: appearance is similar to cystic type with patches of increased density within the lucent lesions

D. hemangioma or AVM of bone or scalp

E. pacchionian depression: arachnoid granulations (older terms: Pacchioni's granulation or pacchionian bodies) resorb CSF into vascular system and occasionally cause a bony lucency, usually near the superior sagittal sinus

F. Albright's syndrome

G. congenital foramina: "holes" in skull traversed by emissary veins

H. parietal thinning: usually a bilateral process

I. frontal fenestrae

J. venous lakes

K. cerebral herniations: AKA occipital pacchionian granulations

- traumatic

  A. surgical defect: burr hole, craniectomy

  B. fracture

  C. post-traumatic leptomeningeal cyst (*see page 892*)

  D. following trauma in children[113]

- inflammatory

  A. osteomyelitis: including tuberculosis[114]

  B. sarcoidosis

  C. syphilis

- neoplastic

  A. hemangioma: fine, honeycombed matrix. Classic x-ray finding: "starburst" appearance due to radiating bone spicules (may occur in as few as ≈ 11% of cases[112])

  B. intracranial tumor with erosion

C. lymphoma, leukemia
D. meningioma
E. metastasis: usually hot on bone scan
F. multiple myeloma, plasmacytoma: *see page 740*. Usually cool on bone scan
G. sarcoma or fibrosarcoma of bone
H. skin tumor with invasion (rodent ulcer)
I. neuroblastoma
J. lipoma
K. epidermoid (may also be considered congenital, thus also *see above*)

• miscellaneous

A. histiocytosis X (eosinophilic granuloma is the mildest form): perfectly round non-sclerotic punched out lesion, generally multiple, tender (*see page 699*)
B. Paget's disease (when seen as a zone of osteolysis without osteoblastic sclerosis on skull films, this is defined as **osteoporosis circumscripta**). Usually "hot" on bone scan
C. aneurysmal bone cyst: rare. Arises in diploë and expands both tables which become thin but remain intact
D. brown tumor of hyperparathyroidism

Diffuse demineralization or destruction of the skull

(including "salt and pepper skull")

• common

1. hyperparathyroidism, primary or secondary
2. metastatic carcinoma or neuroblastoma
3. multiple myeloma
4. osteoporosis

• uncommon

1. Paget's disease (osteoporosis circumscripta)

Diffuse increased density, hyperostosis, or calvarial thickening

• common

1. anemia (sickle cell, iron deficiency, thalassemia, hereditary spherocytosis)
2. fibrous dysplasia
   A. leontiasis ossea ("lion-like facies"): a form of polyostotic fibrous

dysplasia

3. hyperostosis interna generalisata
4. osteoblastic metastases (especially prostate, breast)
5. Paget's disease (begins with lytic zone and diploic thickening)
6. treated hydrocephalus

- uncommon
  1. chronic phenytoin therapy
  2. Engelman's disease (progressive diaphyseal dysplasia)
  3. fluorosis
  4. hypervitaminosis D
  5. hypoparathyroidism, pseudohypoparathyroidism
  6. meningioma
  7. osteogenesis imperfecta
  8. osteopetrosis (*see page 1204*)
  9. secondary polycythemia
  10. syphilitic osteitis
  11. tuberous sclerosis

"Hair-On-End" appearance in skull

- common
  1. congenital hemolytic anemia (e.g. thalassemia, sickle cell, hereditary spherocytosis, pyruvate kinase deficiency)
- uncommon
  1. hemangioma
  2. cyanotic congenital heart disease (with secondary polycythemia)
  3. iron deficiency anemia
  4. metastases: especially neuroblastoma, thyroid carcinoma
  5. multiple myeloma
  6. meningioma
  7. osteosarcoma
  8. polycythemia vera

Focal increased density of skull base

- common
  1. fibrous dysplasia
  2. meningioma

• uncommon
  1. mastoiditis
  2. nasopharyngeal carcinoma
  3. osteoblastic metastasis
  4. osteoma of the outer table or diploe
  5. chondroma
  6. sarcoma of bone (e.g. osteosarcoma, chondrosarcoma)
  7. sphenoid sinusitis

GENERALIZED INCREASED DENSITY OF SKULL BASE

• common
  1. fibrous dysplasia
  2. Paget's disease
• uncommon
  1. severe anemia (e.g. thalassemia, sickle cell)
  2. Engelman's disease (progressive diaphyseal dysplasia)
  3. fluorosis
  4. hyperparathyroidism, primary or secondary (treated)
  5. hypervitaminosis D
  6. idiopathic hypercalcemia
  7. meningioma
  8. osteopetrosis (*see page 1204*)

LOCALIZED INCREASED DENSITY OR HYPEROSTOSIS OF THE CALVARIA

• common
  1. anatomic variation (e.g. sutural sclerosis)
  2. fibrous dysplasia
  3. osteoma (*see page 698*)
  4. meningioma
  5. hyperostosis frontalis interna (*see page 700*)
  6. osteoblastic metastases (especially: prostate, breast)
  7. Paget's disease (begins with lytic zone and diploic thickening)
  8. cephalhematoma
  9. depressed skull fracture
• uncommon
  1. osteosarcoma

2. chronic osteomyelitis, tuberculosis
3. tuberous sclerosis
4. osteoid osteomas: radiolucent nidus with surrounding zone of dense sclerosis
5. osteoblastoma:
6. ossifying fibromas: predilection for frontotemporal region
7. radiation necrosis

PNEUMOCELE

Pneumocele: enlargement of an air sinus often with bone erosion. **Pneumosinus dilatans** generally denotes enlargement of an air sinus without bone erosion, as may occur with tuberculum sellae or planum sphenoidale meningiomas (*see page 1216*).

Pneumoceles occur primarily in the maxillary antrum. Involvement of frontal sinus. usually involves pneumosinus dilatans. Etiology is unknown, and may involve a trap-valve mechanism, ruptured mucocele, or possibly congenital. May occur with fibrous dysplasia.

Presentation of pneumocele or pneumosinus dilatans:

1. headache
2. neuralgia
3. facial asymmetry
4. frontal bossing (with frontal pneumosinus dilatans)
5. exophthalmous
6. CSF fistula (leak)

35.2.11. Combined intracranial/extracranial lesions

Lesion causing mass outside skull with intracranial component.

1. intra-axial: rule of thumb - “there is no intra-axial lesion that grows out of skull”
2. extra-axial:
   - A. meningioma
     1. may arise in diploe, grows outward and inward
     2. intracranial meningioma can grow through bone by destroying it
     3. intracranial meningioma can induce hyperostosis that causes extracranial mass

B. metastatic disease (e.g. GI carcinoma, and especially prostate Ca)

C. bone (skull) lesion:

1. hemangioma
2. epidermoid
3. fibrous dysplasia (rare)
4. giant cell tumor (rare)
5. Ewing's sarcoma (rare in skull)
6. aneurysmal bone cyst (5% occur in skull, occipital bone most common)

35.2.12. Intracranial calcifications

Often due to deposition of calcium in the media of medium-sized blood vessels without compromise of the lumen. Usually asymptomatic. Considered abnormal when present to a significant enough degree to be visible on plain x-ray in a young person.

SINGLE INTRACRANIAL CALCIFICATIONS

1. physiologic
   - A. choroid plexus: calcifications usually bilateral (*see below*)
   - B. arachnoid granulation
   - C. diaphragma sellae
   - D. dural (falcine, tentorial, sagittal sinus)
   - E. habenular commissure
   - F. petroclinoid or interclinoid ligaments
   - G. pineal: 55% of patients > 20 yrs age have a calcified pineal gland visible on plain skull x-ray
2. infection
   - A. cysticercosis cyst: single or multiple (see *Neurocysticercosis*, page 370)
   - B. encephalitis, meningitis, cerebral abscess (acute and healed)
   - C. granuloma (torulosis and other fungi)
   - D. hydatid cyst
   - E. tuberculoma
   - F. paragonimiasis
   - G. rubella

    H. syphilitic gumma
3. vascular
    A. aneurysm, including:
        1. vein of Galen aneurysm
        2. giant aneurysm
    B. arteriosclerosis (especially carotid artery in siphon region)
    C. hemangioma, AVM, Sturge-Weber syndrome
4. neoplastic: calcifications usually suggest a more benign process
    A. meningioma (*see page 613*)
    B. craniopharyngioma
    C. choroid plexus papilloma
    D. ependymoma
    E. glioma (especially oligodendroglioma, also astrocytoma)
    F. ganglioglioma
    G. lipoma of corpus callosum
    H. pinealoma
    I. hamartoma of tuber cinerium
5. miscellaneous
    A. hematoma: ICH, EDH or SDH. Calcifications usually only when chronic
    B. idiopathic
    C. tuberous sclerosis (*see page 725*)

Multiple intracranial calcifications

- common
    A. choroid plexus: the most common site for physiologic calcification (in lateral ventricles where it is usually bilateral and symmetric; rare in 3rd & 4th ventricles). Increases in frequency and extent with age (prevalence: 75% by 5th decade). Rare under age 3. Under age 10, consider possible choroid plexus papilloma. Involvement in the temporal horns is often associated with neurofibromatosis
    B. basal ganglia **(BG)**: slight bilateral BG calcifications on CT are common, especially in the elderly. Considered a normal radiographic variant by some. They may be idiopathic, secondary to conditions such as hypoparathyroidism or long-term anticonvulsant use, or part of rare conditions such as Fahr's disease (*see below*). BG calcifications > 0.5 cm dia are possibly association with cognitive impairment and a high

prevalence of psychiatric symptoms[115]

- uncommon
    A. Fahr's disease: progressive idiopathic calcification of medial portions of basal ganglia, sulcal depths of cerebral cortex, and dentate nuclei[116]
    B. hemangioma, AVM, Sturge-Weber syndrome, von Hippel-Lindau disease
    C. basal cell nevus syndrome (falx, tentorium)
    D. Gorlin's syndrome. Associated findings: mandibular cysts, rib and vertebral deformities, short metacarpals. Medulloblastoma seen in several patients
    E. cytomegalic inclusion disease
    F. encephalitis (e.g. measles, chickenpox, neonatal herpes simplex)
    G. hematomas (SDH or EDH, chronic)
    H. neurofibromatosis (choroid plexi)
    I. toxoplasmosis
    J. tuberculomas; tuberculous meningitis (treated)
    K. tuberous sclerosis
    L. hypoparathyroidism (including post-thyroidectomy cases[117]) and pseudohypoparathyroidism
    M. multiple tumors (e.g. meningiomas, gliomas, metastases)
    N. cysticercosis cyst: may be single or multiple (see *Neurocysticercosis*, page 370)

35.2.13. Intraventricular lesions

Intraventricular tumors represent only ≈ 10% of CNS neoplasms. A clue to differentiating a tumor located within the ventricle from an intraparenchymal tumor invaginating into the ventricle is a "cap" of CSF surrounding an intraventricular tumor on CT or MRI. Differential diagnosis (percentages quoted are from a series of 73 patients with an intraventricular lesion on CT seen at UCSF[118]).

1. **astrocytoma**: (20%) the most common lesion. Hydrocephalus **(HCP)** is present in 73%. Hyperdense on non-contrast CT **(NCCT)** in 77%.
   Locations in descending order of frequency:
   - frontal horn
   - third ventricle

- atrium (AKA trigone)
- fourth ventricle

2. **colloid cyst**: (14%) essentially seen only in anterior third ventricle at foramen of Monro[A]. 50% are hyperdense on NCCT. MRI appearance is variable, and may occasionally be missed. Little or no enhancement on CT/MRI (*see page 665*). DDx includes xanthogranuloma
3. **meningioma**: (12%) most in atrium, rarely in frontal horn. All hyperdense with dense uniform enhancement. May be calcified. Most have dense tumor blush on angiogram, most supplied from anterior choroidal artery, posterior choroidal less common. Thought to arise from arachnoidal cells within the choroid plexus
4. **ependymoma**: (10%) most in 4th ventricle, may occur in body of lateral ventricle. Often hyperdense on CT because of high cellularity
5. **craniopharyngioma**: (7%) primarily in 3rd ventricle. Most have punctate calcification. Squamous epithelial rests in region of lamina terminalis are felt to give rise to this uncommon variety of craniopharyngioma
6. **medulloblastoma**: (5%) often fill 4th ventricle. Hyperdense on CT with homogeneous enhancement
7. **cysticercosis**: (5%) may involve any ventricle or may be panventricular (NB: incidence related to geographic location), *see page 370*
8. **choroid plexus papilloma**: (5%) most common in lateral ventricle (may be bilateral), but also may be seen in 4th and occasionally in 3rd. Non-obstructive HCP may occur (possible CSF overproduction). Intense blush on angiogram
9. **epidermoid**: (4%) mostly in 4th ventricle. Hypodense on CT with no enhancement (tend to follow CSF signal). The most common 4th ventricular low density lesion in the U.S.
10. **dermoid**: (3%) common in 4th ventricle. May see free floating fat in ventricles suggestive of cyst rupture. Tendency to form in midline
11. **choroid plexus carcinoma**: (3%) common in atrium of lateral ventricle. May extended into adjacent brain parenchyma with edema and shift. Intense blush on angio. NB: very rare lesion
12. **subependymoma**: (3%) 4th ventricle or frontal horn. Typically isodense on CT with <u>minimal enhancement</u>. May have calcification or cystic degeneration (more common in ependymoma). Most commonly in floor of 4th ventricle near obex
13. **ependymal cyst**: (3%) common in lateral ventricle. Absence of communication demonstrated by water soluble contrast cisternography

14. **arachnoid cyst**: (1%) lateral ventricle. Absence of communication demonstrated by water soluble contrast cisternography
15. **arteriovenous malformation (AVM)**: (3%)
16. **teratoma:** (1%) Located in anterior 3rd ventricle. Partially calcified with foci of fat density. Marked enhancement
17. central neurocytoma: *see page 612*
18. metastases: breast and lung reported[119]
19. chordoid glioma of the 3rd ventricle[120]

A. other sites have been described but are exceedingly rare

FEATURES TO HELP IDENTIFY TYPE OF INTRAVENTRICULAR LESIONS

By location within ventricular system

Table 35-7 shows the breakdown of lesion type by location within the ventricular system.

Table 35-7 Type of intraventricular lesions by location[118]
(numbers are patients out of 73*)

3rd ventricle		4th ventricle		Lateral ventricle: Atrium		Lateral ventricle: Body		Lateral ventricle: Frontal horn	
colloid cyst	10	medulloblast.	4	meningioma	8	ependymoma	3	astrocytoma	7
craniopharyng	5	ependymoma	4	astrocytoma	3	ch. plexus papil.†	1	meningioma	1
astrocytoma	4	epidermoid	3	ch. plexus papil.	1	ch. plexus carc.	1	subependym.	1
teratoma	1	cysticercosis	2	ch. plexus carc.	1	ependym. cyst	1	dermoid	1
ch. plexus papil.	1	astrocytoma	1	arachnoid cyst	1	AVM	1		
cysticercosis	1	subependym.	1	ependym. cyst	1				
dermoid	1								
ch. plexus carc.	1								
AVM	1								

* 1 patient had cysticercosis diffusely throughout ventricles
† 1 patient with bilateral lateral ventricle papillomas

By location and age within <u>lateral ventricle</u>[121]

See *Table 35-8*. This study excluded tumors that were clearly arising in the third ventricle or were predominantly parenchymal with intraventricular extension.

The teratoma and both PNETs occurred in age < 1 year, and all showed calcifications. Only one CPP occurred above age 5 years.

In adults > 30 years age, the only tumors found in the trigone were meningiomas. Subependymomas were the only nonenhancing tumor in this age group.

Table 35-8 Lateral ventricle tumor type by location & age

Age (yrs)	------- Location within lateral ventricle* -------		
	Foramen of Monro region	Trigone	Body
0-5	0	8 CPP	2 PNETs 1 teratoma
6-30	5 SGCAs 2 pilocytic astrocytomas 1 CPP 1 meningioma 1 oligodendroglioma	1 ependymoma 1 oligodendroglioma	1 mixed glioma 1 ependymoma 1 pilocytic astrocytoma
> 30	2 metastases	8 meningiomas	2 glioblastomas 1 lymphoma 1 metastasis 6 subependymomas

* abbreviations: CPP = choroid plexus papillomas, PNET = primitive neuroectodermal tumor, SGCA = subependymal giant cell astrocytoma

By location within third ventricle

- anterior third ventricle
  1. colloid cyst
  2. sellar mass
  3. sarcoidosis
  4. aneurysm
  5. hypothalamic glioma
  6. histiocytosis
  7. meningioma
  8. optic glioma
- posterior third ventricle
  1. pinealoma (dysgerminoma)
  2. meningioma
  3. arachnoid cyst
  4. vein of Galen aneurysm

By enhancement

All lesions enhanced except: cysts (ependymal and arachnoid), dermoids and epidermoids. There are differences of opinion of the tendency for subependymomas to enhance, Jelinek et al.[121] found that they did not.

By multiplicity

Multiple lesions are more suggestive of: neurocysticercosis, metastases, a ruptured epidermoid cyst.

35.2.14. Periventricular lesions

Periventricular solid enhancing lesions on CT (in decreasing frequency)

1. **lymphoma** (CNS involvement from systemic, or rarely primary brain): must be included in differential diagnosis of any solid enhancing periventricular brain tumor (*see page 672*). Very radiosensitive
2. ependymoma (usually invaginates)
3. metastatic Ca: especially malignant melanoma or choriocarcinoma
4. ventriculitis
5. medulloblastoma (in peds), AKA cerebellar sarcoma in adults
6. pineal tumor (dysgerminoma type): usually midline, young patient
7. occasionally, glioblastoma can present like this

Periventricular low density on CT, or high signal on T2WI MRI

1. increased extracellular or intracellular water content (edema)
   - A. in hydrocephalus: transependymal CSF absorption (see footnote *page 310*)
   - B. necrosis from infarction
   - C. edema from tumor
2. uncommon late variants of adrenoleukodystrophy
3. vascular disorders
   - A. subacute arteriosclerotic encephalopathy (**Binswanger's disease**)[122,

[123]

   B. cerebral embolism
   C. vasculitis
   D. amyloid angiopathy
   E. low flow states
4. demyelination: including multiple sclerosis
5. **leukoaraiosis** 124: white matter disease with symmetric (or nearly so) periventricular white matter changes on CT or MRI. May be asymptomatic or may present with findings including dementia. May be related to:
   A. Binswanger's encephalopathy
   B. watershed infarction[125]
   C. normal aging[126]: increases each decade after age 60, usually patchy
   D. hypoxia
   E. hypoglycemia[127]
6. heterotopias: islands of grey matter in abnormal locations
7. following radiation therapy **(XRT)**

35.2.15. Meningeal thickening/enhancement

Two main categories of enhancement[128]:

1. dural enhancement: visible beneath the inner table of the skull. Does not follow the gyral convolutions. May be either:
   A. focal
      1. adjacent to meningioma: so called "dural tail"
      2. pleomorphic xanthoastrocytoma: also can have "dural tail"
   B. diffuse dural enhancement[129]: associated with extraaxial neoplastic processes in ≈ 65%. Clinically: H/A, multiple cranial nerve palsies, seizures; may be indistinguishable from leptomeningeal metastases
      1. intracranial hypotension: diffuse pachymeningeal enhancement on cerebral MRI (*see page 305*)
      2. bacterial meningitis
      3. primary CNS tumors: medulloblastoma, malignant meningioma
      4. sarcoidosis
      5. following craniotomy
      6. metastases (mostly carcinomas):
         a. bony mets to skull: present in 10 of 13 patients

b. dural metastases
c. leptomeningeal
7. following subdural hemorrhage[130]
2. leptomeningeal: may be either:
   A. thin linear enhancement that closely follows the gyri
   B. small nodules attached to the brain

35.2.16. Ependymal and subependymal enhancement

Some overlap with periventricular enhancement. Ependymal enhancement often heralds a serious condition[131]. Main DDx is tumor vs. infectious process.

1. ventriculitis or ependymitis: ependymal enhancement occurs in 64% of cases of pyogenic ventriculitis[132]. Infection may occur in the following settings
   A. following shunt surgery
   B. after intraventricular surgery
   C. with indwelling prosthetic devices (e.g. Ommaya reservoir)
   D. with use of intrathecal chemotherapy
   E. with meningitis
   F. with viral ependymitis
   G. in some cases of CMV encephalitis in immunocompromised patients
   H. granulomatous involvement: esp. in immunocompromised patients; e.g. tuberculosis, mycobacterium, syphilis
2. lymphoproliferative disorders
   A. CNS lymphoma: *see page 672*
   B. leukemia
3. metastasis
4. carcinomatous meningitis: typically also produces meningeal enhancement (*see page 711*)
5. multiple sclerosis: usually more *peri* ventricular (in the white matter)
6. transient enhancement reported in a child with ependymoma in the absence of tumor spread[133]
7. tuberous sclerosis: subependymal hamartomas appear as nodules which occasionally enhance (*see page 725*). These gradually calcify with age

Immunocompromised patients: DDX is mainly lymphoma vs. viral

ependymitis[131]. The enhancement pattern is helpful[131]:

1. thin linear enhancement: suggests virus (CMV or varicella-zoster)
2. nodular enhancement: suggests CNS lymphoma
3. band enhancement: less specific (may occur with virus, lymphoma, or TB)

Immune competent patients[131]:

1. infection
   A. bacterial (pyogenic) ventriculitis
   B. tuberculous ventriculitis
   C. cystic lesions suggest cysticercosis
2. in the absence of constitutional symptoms
   A. lymphoma
   B. ependymoma
   C. germ cell tumor
   D. metastases
3. in the presence of appropriate constitutional symptoms: linear enhancement is rarely due to neurosarcoidosis or Whipple's disease, metastatic multiple myeloma (usually nodular)

35.2.17. Intraventricular hemorrhage

Etiologies:

1. most occur as a result of extension of intraparenchymal hemorrhages
   A. in the adult:
1. spontaneous ICH: especially thalamic or putaminal (*see page 1118*)
2. associated with AVM
   B. in newborns: extension of subependymal hemorrhage (*see page 1131*)
2. <u>pure</u> intraventricular hemorrhage **(IVH)** is usually the result of a rupture of
   A. aneurysm: accounts for ≈ 25% of IVH in adults, and is second only to extension of intracerebral hemorrhage as the most common cause. IVH occurs in 13-28% of ruptured aneurysms in clinical series[134]. More common with the following aneurysms: a-comm, distal basilar artery or carotid terminus, VA or distal PICA (*see page 1056* for patterns)
   B. vertebral artery dissection (or dissecting aneurysms): *see page 1163*
   C. intraventricular AVM

D. intraventricular tumor

35.2.18. Medial temporal lobe lesions

May be responsible for seizures, especially "uncal fits" (temporal lobe seizures).

1. hamartoma
2. mesial temporal sclerosis: should see atrophy of the parenchyma in this area with dilatation of the temporal horn of the lateral ventricle (*see page 395*)
3. glioma: may be low grade. Look for mass effect and possibly enhancement

35.2.19. Basal ganglion abnormalities

1. generally symmetric abnormalities
    A. calcification: *see page 1224*
    B. Wilson's disease (hepatolenticular degeneration): autosomal recessive disease causing accumulation of copper in tissues
    C. Huntington's disease (or chorea): caused by > 40 trinucelotide CAG repeats in the Huntington gene (4p[16].3) which leads to the production of the protein huntingtin. Cell loss in caudate nucleus can be seen on CT or MRI
    D. manganese: symmetrical high signal abnormalities on T1WI primarily in the globus pallidus with essentially no findings on T2WI or GRASS (almost pathognomonic) - *see page 60*
    E. globus pallidus (low density on CT):
        1. severe carbon monoxide intoxication
        2. cyanide poisoning
        3. hypoxia
    F. putamen
        1. hypoglycemia: affects corpus striatum (caudate and putamen)
2. stroke

35.2.20. Thalamic lesions

Astrocytomas are the most common tumors.

1. common neoplasms

Adults	Pediatrics
A. anaplastic astrocytoma	anaplastic astrocytoma
B. glioblastoma multiforme	astrocytoma (WHO grade II)
C. metastasis	glioblastoma multiforme
D. primary CNS lymphoma	pilocytic astrocytoma

2. uncommon neoplasms

Adults	Pediatrics
A. astrocytoma (WHO grade II)	germinoma
B. neurocytoma	glioblastoma multiforme
C. oligodendroglioma	PNET
D. pilocytic astrocytoma	subependymal giant cell tumor
E. hamartoma	

3. non-neoplastic (pediatric and adult)
   - A. cavernous angioma
   - B. granuloma
   - C. heterotopias
   - D. AVM
   - E. infarct

35.2.21. Intranasal/intracranial lesions

Lesions within the nose that may communicate with the intracranial cavity:

1. infectious
   - A. tuberculosis
   - B. syphilis
   - C. Hansen's disease (leprosy)
   - D. fungal infections, especially:
     1. aspergillosis
     2. mucormycosis: seen primarily in diabetics or immunocompromised patients (*see page 836*)
     3. *Sporothrix schenckii*

    4. *Coccidioides*
  - E. Wegener’s granulomatosis: (*see page 78*) necrotizing granulomatous vasculitis of the upper and lower respiratory tracts with glomerulonephritis and nasal destruction[135]
  - F. lethal midline granuloma: (*see page 78*) a locally destructive lymphomatoid infiltrative disease that may not have true granulomas, and may also cause local nasal destruction. However, renal and tracheal involvement do not occur as in Wegener’s granulomatosis
  - G. polymorphic reticulosis: may be a nasal lymphoma. Possibly the same disease as lethal midline granuloma (*see above*)
2. mucocele: a retention cyst of an air sinus that results from an occluded ostium and may cause expansive erosion of the involved sinus. Often enhances with IV contrast (MRI or CT), and may contain mucus or pus
3. neoplasms
  - A. carcinoma of the nasal sinus
    1. squamous cell
    2. glandular
    3. nasopharyngeal carcinomas: may be related to Epstein-Barr Virus **(EBV)** infection
    4. sinonasal undifferentiated carcinoma **(SNUC)**[136]: distinct from lymphoepithelioma (less keratinizing). Rare, aggressive carcinoma (more lethal variant of squamous cell carcinoma) with poor prognosis. Incidence may be higher with prior XRT and in woodworkers and nickel factory workers. May invade adjacent structures, those relevant to neurosurgeons: frontal fossa, and cavernous sinus. No relation to EBV. Treatment: tri-modal therapy (XRT, chemotherapy and salvage surgery)
  - B. **esthesioneuroblastoma** 137 or aesthesioneuroblastoma AKA olfactory neuroblastoma: named for the stem cell of the olfactory epithelium (esthesioneuroblast). A malignant tumor arising from crest cells of the nasal vault, often with intracranial invasion. Very rare (≈ 200 reported cases). Presents with epistaxis (76%), nasal obstruction (71%), tearing (14%), pain (11%), diplopia, proptosis, anosmia and endocrinopathies[138]. Treatment: surgical resection followed by XRT, ± chemotherapy
  - C. metastatic tumors: very rare, possibly with renal cell carcinoma
  - D. benign tumors
    1. frontal meningioma: rarely erodes into nasal cavity

   2. rhabdomyoma
   3. benign hemangiopericytoma
   4. cholesteatoma
   5. chordoma
4. congenital lesions
   A. **encephalocele** (*see page 232*): a nasal polypoid mass in a newborn should be considered an encephalocele until proven otherwise. Classifications:
      1. cranial vault
      2. frontal ethmoidal
      3. basal
      4. posterior fossa
   B. **nasal glioma**: non-neo-plastic glial tissue located within the nose, often conceptually and diagnostically confused with an encephalocele (*see Table 35-9*). The term "glioma" is a misnomer, and nasal glial heterotopia is preferred. Does not communicate with the subarachnoid space

Table 35-9 Encephalocele vs. nasal glioma

Finding	Encephalocele	Nasal glioma
pulsatile?	frequently (may not be if small)	no
changes with Valsalva maneuver	swells (Furstenberg sign)	no change
presence of hypertelorism	suggests encephalocele	does not correlate
attachment to CNS	stalk	none, or minimal
probe	can be passed lateral	cannot be passed lateral

35.2.22. Spine

35.2.22.1. Atlantoaxial subluxation

1. incompetence of the transverse atlantal ligament **(TAL)**: results in increased atlanto-dental interval **(ADI)** (*see page 136*)
   A. rheumatoid arthritis: erosion of insertion points of the TAL (*see page 495*)
   B. traumatic (*see page 957*)
      1. disruption (tear) of the TAL (rare)

        2. avulsion of the insertion points of the TAL (as in comminuted C1 fx)
    C. congenital laxity of the TAL:
        1. Down syndrome: 20% incidence[139] (*see page 498*)
        2. may be associated with neurofibromatosis
    D. retropharyngeal infections: chronic tonsillitis, Grisel syndrome (*see page 956*)
    E. chronic steroid use
2. incompetence of the odontoid process: ADI is <u>normal</u>
    A. odontoid fractures: *see page 963*
    B. os odontoideum: *see page 966*
    C. erosion of the odontoid due to rheumatoid arthritis (RA): *see page 495*
    D. neoplastic erosion of the odontoid:
        1. metastases to the upper cervical spine (*see page 743*)
        2. other tumors of the axis (*see below*)
    E. Morquio syndrome: hypoplasia of the dens (*see page 494*)
    F. congenital absence/dysplasia of the odontoid
    G. following transoral odontoidectomy: (*see page 176*)
    H. local infection

Chronic AAS seen in conditions such as rheumatoid arthritis or Down syndrome may be significant yet asymptomatic. Treatment decisions in this group are difficult. *Acute* AAS is more commonly symptomatic and may be life threatening.

35.2.22.2. Abnormalities in vertebral bodies

For lesions unique to the craniocervical junction & upper cervical spine, *see page 494*. For abnormalities unique to the axis (C2), *see below*.

1. neoplasms (for more extensive list, *see page 728*)
    A. metastases: prostate, breast, lung, renal cell, thyroid, lymphoma & myeloma commonly go to bone. Four patterns (≈ all are <u>low intensity</u> on T1WI):
        1. focal lytic (most common): T1WI = hypointense, T2WI = hyperintense
        2. focal sclerotic: hypointense on T1WI *and* T2WI
        3. diffuse homogeneous: T1WI = hypointense, T2WI = hyperintense

or heterogeneous
        4. diffuse heterogeneous: mixed signal intensities on T1WI & T2WI
    B. primary bone tumors (*see page 736* for more extensive discussion)
        1. vertebral hemangioma
        2. osteoblastoma
2. infection: osteomyelitis/discitis
3. **fatty infiltrate** or replacement of bone marrow: with age, hematopoietic red marrow of VBs is gradually replaced by yellow marrow in a splotchy pattern at a slower rate than in many other locations, e.g. distal appendicular bones[140]. T1WI: yellow marrow (MRI characteristics similar to subcutaneous fat) is hyperintense to red marrow (caution: bright areas on T1WI may be fat, or may be a normal area next to a low intensity met). T2WI: yellow marrow is bright
4. degenerative changes (Modic changes): *see page 430*
5. metabolic
    A. Paget's disease: plain x-rays → enlargement of VBs with cortical thickening usually involving several contiguous levels (*see page 499*)
    B. osteoporosis: reduced bone density. Vertebral compression fractures may be seen
    C. ankylosing spondylitis: osteoporotic VBs, calcified intervertebral discs (sparing the nucleus pulposus), and ossified ligaments, → square VBs with bridging syndesmophytes ("bamboo spine") (*see page 502*). Starts in sacroiliac joints & lumbar spine

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35.2.22.3. Axis (C2) vertebra lesions

1. tumors: rare. Possibilities include those that involve the spine at any location (*see page 728*). Some factors pertinent to this location[141]:
    A. primary bone
        1. chondroma
        2. chondrosarcoma: rare in the craniovertebral junction. Lobulated tumors with calcified areas
        3. chordoma: slow-growing radioresistant malignancy (*see page 675*)
        4. osteochondroma (chondroma)
        5. osteoblastoma: *see page 736*
        6. osteoid osteoma (*see page 736*): more common in posterior elements than VB[142]
        7. giant-cell tumors of bone: typically arise in adolescence. Lytic with

bony collapse[143]

B. metastatic: including
   1. typical metastases that spread hematogenously to bone, including:
      a. breast cancer
      b. prostate cancer
      c. malignant melanoma
      d. paraganglioma
      e. renal cell carcinoma
   2. extension of regional tumors
      a. nasopharyngeal tumors
      b. craniopharyngioma

C. miscellaneous
   1. plasmacytoma
   2. multiple myeloma
   3. eosinophilic granuloma: osteolytic defect with progressive vertebral collapse. Occasionally occur in C2144
   4. Ewing's sarcoma: malignant. Peak incidence during 2nd decade of life
   5. aneurysmal bone cyst[145]

2. infection: osteomyelitis of the axis
3. pannus from old nonunion of fracture or from rheumatoid arthritis **(RA)**
4. erosive changes in the odontoid process with RA (*see page 495*)

35.2.22.4. Pathologic fractures of the spine

Fractures due to metastatic involvement are hypointense on T1WI and hyperintense on T2WI. Benign VB collapse should be isointense to normal VBs on all sequences[146, 147] and the VB should look homogeneous. On T2WI or STIR images, the cortex of the VB (which should be dark border around the VB due to low water content of cortical bone) should be intact.

Etiologies:

1. osteoporosis
2. neoplasm: short list (*see page 736* for the long list)
   A. metastases: common sources of spine mets: lung, breast, prostate, myeloma
   B. eosinophilic granuloma (*see page 729*): may cause vertebra plana (*see below*)

        C. lymphoma
        D. hemangioma: *see page 738*
3. infection
4. avascular necrosis of the vertebral body
    A. Calve-Kummel-Verneuil disease (*see below*)
    B. with steroid use

Vertebra plana

Criteria:

1. uniform collapse of vertebral body into flat thin disc
2. increased density of vertebra
3. spares neural arches
4. normal disc and intervertebral disc space
5. intervertebral vacuum cleft sign (pathognomonic)
6. no kyphosis

Etiologies include:

1. eosinophilic granuloma
2. Calve-Kummel-Verneuil disease: avascular necrosis of the vertebral body. Occurs in 2-15 year olds
3. hemangioma

35.2.22.5. Spinal epidural masses

See items marked with a dagger (†) under *Myelopathy* on page 1185.

35.2.22.6. Destructive lesions of the spine

1. neoplastic (see *Differential diagnosis: spine & spinal cord tumors*, page 728 for more):
    A. metastatic tumors with a predilection for bone: prostate, breast, renal cell, lymphoma, thyroid, lung… (see *Spinal epidural metastases*, page 742)
    B. primary bone tumors: chordomas (*see page 675*), osteoid osteoma (*see page 736*), hemangioma (*see page 738*)
2. infection:
    A. vertebral osteomyelitis: occurs mostly in IV drug abusers, patients

with diabetes mellitus, and hemodialysis patients. May have associated spinal epidural abscess. Also see *Vertebral osteomyelitis*, page 380

B. discitis (see *Discitis*, page 383)

3. chronic renal failure: some patients develop a destructive spondyloarthropathy that resembles infection[148, 149]
4. ankylosing spondylitis: bamboo spine (square VBs with bridging syndesmophytes) - *see page 502*
5. lesions producing <u>posterior</u> scalloping of VB (mnemonic: AMEN)

A acromegaly or achondroplasia

M Marfan syndrome or mucopolysaccharidosis E Ehlers-Danlos

N neurofibromatosis

• also: dural ectasia

6. lesions producing <u>anterior</u> scalloping of VB

A. aortic aneurysm

B. lymphoma

C. spinal TB

<u>DIFFERENTIATING FACTORS</u>

Of the many lytic or destructive lesions that involve the vertebra, destruction of the disc space is highly suggestive of <u>infection</u> which often involves at least two adjacent vertebral levels. Although tumors may involve adjacent vertebral levels and cause collapse of disc height, the disc space is usually not destroyed[150] (possible exceptions include: some vertebral plasmacytomas, a reported metastatic cervical carcinoma, and there may occasionally be destruction of the disc in ankylosing spondylitis[151]). Unlike pyogenic infections, the disc may be relatively resistant to tuberculous involvement in Pott's disease[152]. Also, since metastatic tumor involvement usually produces widespread bony involvement, it is less likely with involvement of a single bone.

35.2.22.7. Vertebral hyperostosis

1. Paget's disease: classic "ivory bone" with cortical thickening ("picture frame" appearance on plain x-rays). Consider Paget's with a <u>dense</u> vertebra on x-ray in an older patient, commonly involving several contiguous vertebrae (*see page 498*)
2. osteoblastic metastases

A. in men: prostate

B. in women: breast
C. lymphoma

35.2.22.8. Sacral lesions

1. tumors
   A. metastases: the most common sacral neoplasm
   B. primary neoplasms of the sacrum are uncommon and include:
      1. giant cell tumor: *see* *page 742*
      2. chordoma
      3. teratoma:
         a. adults: pre-sacral or sacro-coccygeal teratomas may arise from cells sequestered from Hensen's node in the caudal embryo. Rarely cause neurologic involvement (distinguishing this from chordoma). Sacrum may be normal in up to 50% (abnormal in almost all chordomas). Treatment is complete removal usually by general surgeon
         b. peds: malignant pre-sacral teratoma is a rare tumor seen primarily in female children
2. infection: most infections of the sacrum or sacroiliac joint are due to contiguous spread from a suppurative focus
3. arthritic disorders
   A. ankylosing spondylitis: (*see* *page 502*) involves SI joint almost by definition
   B. osteoarthritis
4. sacral fractures: may be due to
   A. trauma
   B. repetitive stress
   C. sacral insufficiency: *see* *page 1193*
5. congenital
   A. sacral agenesis (caudal regression syndrome): rare (prevalence: 0.005-0.01%; higher (0.1-0.2%) in children of diabetic mothers (16-20% of children with sacral agenesis have diabetic mothers)). Increased incidence of associated spinal abnormalities including: syrinx, tethered cord, lipoma, and lipomyelomeningocele.
      1. Four types:
         Type 1: partial unilateral agenesis, localized to the sacrum or coccyx

Type 2: partial bilaterally symmetric defects in the sacrum. Iliac bones articulate with S1, and distal segments of the sacrum and coccyx fail to develop

Type 3: total sacral agenesis + iliac bones articulate with the lowest segment of the lumbar spine present

Type 4: total sacral agenesis + iliac bones fused posteriorly along the midline

2. in cases of total sacral agenesis (types 3 & 4), MR findings include: absence of the sacrum and coccyx and variable absence of a portion of the lumbar spine, with a characteristic club-shaped configuration of the conus medullaris

6. miscellaneous
   A. osteitis condensans ilii: increased density in ilium, usually asymptomatic (incidental) finding. Occasionally may produce low back pain or tenderness

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35.2.22.9. Enhancing nerve roots

1. tumor
   A. meningeal carcinomatosis
   B. lymphoma
2. infection: especially CMV (often seen in AIDS patients)
3. inflammatory
   A. Guillain-Barre
   B. arachnoiditis
   C. sarcoid

35.2.22.10. Nodular enhancing lesions in the spinal canal

1. neurofibromatosis (NFT)
2. tumor
   A. drop mets
   B. neurofibroma
   C. schwannoma

35.2.22.11. Intraspinal cysts

1. spinal meningeal cysts: *see page 509*

2. cystic neurofibroma:
3. ependymoma: may be cystic. In filum terminale: myxopapillary ependymoma (*see page 731*)
4. syringomyelia: *see page 510*
5. dilated central canal: *see page 510*

35.2.22.12. Diffuse enhancement of nerve roots/cauda equina

(As distinct from nodular enhancement, *see above*)

1. Guillain-Barre (*see page 66*)
2. meningitis
3. cytomegalovirus (CMV) (especially in AIDS)
4. lymphoma
5. sarcoid (look for hilar adenopathy)

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NOTES

Handbook of Neurosurgery 7ed Quick Reference Tables 1

GARDNER/ROBERTSON HEARING (PAGE 623)

Class	Description	Audiogram (dB)	Speech discrimination
I	good-excellent	0-30	70-100%
II	serviceable	31-50	50-59%
III	nonserviceable	51-90	5-49%
IV	poor	91-max	1-4%
V	none	not testable	0

AAO-HNS HEARING (PAGE 623)

Class	Description	Pure tone threshold (dB)		Speech discrimination
A	useful	≤ 30	AND	≥ 70%
B	useful	> 30 AND ≤ 50	AND	≥ 50%
C	aidable	> 50	AND	≥ 50%
D	nonfunctional	any level		< 50%

HOUSE-BRACKMANN VII GRADE (PAGE 622)

Grade	Dysfunction	Description
1	none (normal)	normal function in all areas
2	mild	slight weakness on close inspection
3	moderate	obvious but not disfiguring
4	moderate-severe	obvious weakness &/or disfiguring asymmetry
5	severe	barely perceptible motion
6	total paralysis	no movement

KARNOFSKY SCALE (PAGE 1182)

Score	Meaning
100	normal; no complaints, no evidence of disease
90	able to carry on normal activity; minor symptoms
80	normal activity with effort; some symptoms
70	cares for self; unable to carry on normal activity
60	requires occasional assistance; cares for most needs
50	requires considerable assistance and frequent care
40	disabled; requires special care and assistance
30	severely disabled; hospitalized, death not imminent
20	very sick; active supportive care needed
10	moribund; fatal processes are progressing rapidly

Better prognosis with malignant glioma (PAGE 602)

BRAIN DEATH EXAM (PAGE 289)

1. absence of brainstem reflexes
   - A. fixed pupils (no response to light)
   - B. absent corneal reflexes
   - C. absent oculovestibular reflex (calorics)
   - D. absent oculocephalic reflex (doll's eyes)
   - E. absent gag & cough reflex
2. apnea with arterial pCO2 > 60 mm Hg
3. no response to deep central pain
4. vital signs & general criteria
   - A. core temp > 32.2° C (90° F)
   - B. SBP ≥ 90 mm Hg
   - C. no drugs that could simulate brain death

LUMBAR DISC SYNDROMES (PAGE 445)

Nerve root	L4	L5	S1
Typical HLD	L3-4	L4-5	L5-S1
Pain	anterior thigh	posterior LE	posterior LE, to heel
Weakness	quadriceps	EHL, AT	gastrocnemius
Sensory loss	medial malleolus	dorsum of foot	lateral foot
Reflex	patellar	none	achilles

CERVICAL DISC SYNDROMES (PAGE 461)

Nerve root	C5	C6	C7
Typical HCD	C4-5	C5-6	C6-7
Pain & sensory loss	shoulder	upper arm, thumb, radial forearm	index & middle fingers
Weakness	deltoid	biceps	triceps
Reflex change		biceps	triceps

MUSCLE STRENGTH (PAGE 786)

Grade	Strength	
0	no contraction	
1	flicker or trace contraction	
2	movement with gravity eliminated	
3	movement against gravity	4 – slight resistance
4	movement against resistance	4 moderate resistance
5	normal strength	4 + strong resistance

CLINICAL CRITERIA FOR SPINE STABILITY (PAGE 934)

(no C-spine imaging/x-rays needed)

- awake, alert, oriented (no mental status changes, including no alcohol or drug intoxication)
- no neck pain (with no distracting pain)
- no neurologic deficits

PREVERTEBRAL SOFT TISSUE (PAGE 137)

Space	Level	Maximum normal (mm)		
		Adults		Peds
		MDCT	Lateral x-ray	
retropharyngeal	C1	8.5	10	unreliable
" " "	C2-4	6 – 7*	5 – 7	
retrotracheal	C5-7	18	22	14

* CT data unreliable at C4

ASIA SCI IMPAIRMENT (PAGE 947)

Grade	Description
A	**Complete**: no motor or sensory function preserved
B	Incomplete: **sensory** but no motor function preserved below the neurologic level (includes sacral segments S4-5)
C	Incomplete **motor**: > 50% of key muscles below the neurologic level have a muscle strength grade < 3)
D	Incomplete **motor**: > 50% of key muscles below the neurologic level have a muscle strength grade ≥ 3)
E	**Normal**: Sensory & motor function normal

TLICS THORACOLUMBAR FX. (PAGE 990)

Category	Finding	Points
Radiographic	compression fx	1
	burst component or lateral angulation > 15°	1
	distraction injury	2
	translational/rotational injury	3
Neurologic	intact	0
	root injury	2
	complete SCI	2
	incomplete SCI	3
	cauda equina syndrome	3
Posterior ligament complex	intact	0
	undetermined	2
	definite injury	3

SLIC SUBAXIAL C-SPINE FX. (PAGE 969)
(rate the most severe injury at that level)

Morphology	Points
No abnormality	0
Simple compression (compression fx, endplate disruption, sagittal or coronal plane VB fx.)	1
Burst fracture	2
Distraction (perched facet, posterior element fx.)	3
Rotation/translation (facet dislocation, teardrop fx., advanced compression injury, bilateral pedicle fx., floating lateral mass, relative axial rotation ≥ 11° or any translation not related to degenerative causes)	4
Discoligamentous complex (DLC)	
Intact	0
Indeterminate	1
Disrupted	2
Neurologic status	
Intact	0
Root injury	1
Complete spinal cord injury	2
Incomplete spinal cord injury	3
• Continuous cord compression with neuro deficit	+1

TLICS or SLIC	Management
≤ 3	nonoperative candidate
4	"grey zone"
≥ 5	surgical candidate

GLASGOW COMA SCALE (PAGE 279)

Points	Best eye	Best verbal	Best motor
6	-	-	obeys
5	-	oriented	localizes pain
4	spontaneous	confused	withdraws to pain
3	to speech	inappropriate	flexor (decorticate)
2	to pain	incomprehensible	extensor (decerebrate)
1	none	none	none

CHILDREN'S COMA SCALE (AGE < 4 yrs) (PAGE 279)

Points	Best eye	Best verbal		Best motor
6	-	-		obeys
5	-	smiles, oriented to sound follows objects, interacts		localizes pain
		Crying	**Interaction**	
4	spontaneous	consolable	inappropriate	withdraws to pain
3	to speech	inconsistently consolable	moaning	flexor (decorticate)
2	to pain	inconsolable	restless	extensor (decerebrate)
1	none	none	none	none

STROKE MANAGEMENT TIMELINE (PAGE 1016)

* option for failures with NIHSS > 8-10

** from 6-8 hrs, check perfusion before mechanical embolectomy

TREATMENT OF ACUTE ↑ ICP (PAGE 878)

Check airway, head midline, neck not compressed, HOB @ 30°, afebrile. For resistant or sudden IC-HTN, consider STAT unenhanced head CT
Make sure patient is sedated and paralyzed
Drain 3-5 ml of CSF (if IVC is present)
Osmotic therapy: either mannitol 1 gm/kg or 10-20 ml of 23.4% saline
Hyperventilate: to $PaCO_2$ 30-35 mm Hg
Pentobarb coma

STATUS EPILEPTICUS (PAGE 405)

Summary of AEDs for adults (see text for details)
Lorazepam (Ativan®) **0.1 mg/kg** mg IV slowly @ < 2 mg/min
Either simultaneously with above, or, if seizures persist after 1 minute following completion of lorazepam: **phenytoin/phosphenytoin 20 mg/kg IV** (max rate for phenytoin is < 50 mg/min; for phosphenytoin is < 150 mg/min)
3rd line AEDS: only 7% chance of stopping seizures: phenobarbital up to 20 mg/kg IV @ < 100 mg/min or valproate 15-30 mg/kg IV @ < 6 mg/kg/min or levetiracetam 20 mg/kg IV over 15 mins
Option: skip 3rd line AEDS and intubate and start continuous infusion of: midazolam, pentobarbital or propofol

HUNT-HESS SAH CLASSIFICATION (PAGE 1040)

Grade	Description
0	unruptured aneurysm
1	asymptomatic, or mild H/A and slight nuchal rigidity
1a	no acute meningeal/brain reaction, but with fixed neuro deficit
2	Cr. N. palsy (e.g. III, IV), moderate to severe H/A, nuchal rigidity
3	mild focal deficit, lethargy or confusion
4	stupor, moderate to severe hemiparesis, early decerebrate
5	rigidity deep coma, decerebrate rigidity, moribund appearance
Add one grade for serious systemic disease (e.g. HTN, DM, severe atherosclerosis, COPD) or severe vasospasm on arteriography	

FISHER GRADE (FOR VASOSPASM) (PAGE 1046)

Group	Blood on CT
1	no blood detected
2	diffuse or vertical layers < 1 mm thick
3	localized clot and/or vertical layer ≥ 1 mm
4	intracerebral or intraventricular clot with diffuse or no SAH

SPETZLER-MARTIN AVM GRADING (PAGE 1101)

Graded feature		Points
Size	small (< 3 cm)	1
	medium (3-6 cm)	2
	large (> 6 cm)	3
Eloquence of adjacent brain	non-eloquent	0
	eloquent	1
Venous drainage	superficial only	0
	deep	1

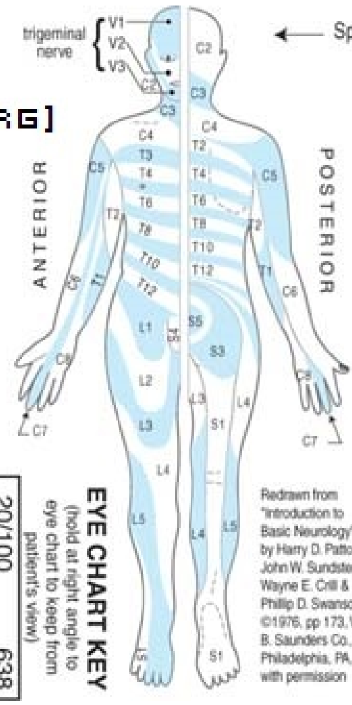
WFNS SAH GRADE (PAGE 1040)

WFNS Grade	GCS Score	Major focal deficit
0	(intact aneurysm)	
1	15	–
2	13-14	–
3	13-14	+
4	7-12	±
5	3-6	±

ICH SCORE (PAGE 1126)

Feature	Finding	Points
GCS Score	3-4	2
	5-12	1
	13-15	0
Age	≥ 80	1
	< 80	0
Location	infratentorial	1
	supratentorial	0
ICH Volume	≥ 30 cc	1
	< 30 cc	0
IVH	yes	1
	no	0

ICH Score	30 day Mortality
0	0%
1	13%
2	26%
3	72%
4	97%
5	100%
6	? 100%



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Spinal nerve root sensory dermatomes (see page 94)

Spinal nerve root motor distribution (see page 945)

Segment	Muscle	Action to test	Reflex
C1-4	neck muscles		
C3, 4, 5	diaphragm	inspiration, FEV1…	
C5, 6	deltoid	abduct arm > 90°	
" "	biceps	elbow flexion	biceps
C6, 7	extensor carpi radialis	wrist extension	supinator
C7, 8	triceps	elbow extension	triceps
" "	extensor digitorum	finger extension	
C8, T1	flexor dig. profundus	grasp (flex DIP)	
" "	hand intrinsics	abduct little finger	
T2-9	intercostals		
T9, 10	upper abdominals	Beevor's sign	abdominal cutaneous
T11, 12	lower abdominals	Beevor's sign	abdominal cutaneous
L2, 3	iliopsoas	hip flexion	cremasteric reflex
L3, 4	quadriceps	knee extension	quadriceps (knee jerk)
L4, 5	medial hamstrings		± medial hamstrings
" "	tibialis anterior	ankle dorsiflexion	
L5, S1	lateral hamstrings	knee flexion	
" "	posterior tibialis	foot inversion	
" "	extensor hallucis longus	great toe extension	
S1, 2	gastrocnemius	ankle plantarflexion	achilles (ankle jerk)
S2, 3	flexor digitorum		
S2-4	bladder, lower bowel anal sphincter	clamp down during rectal exam	anal cutaneous reflex, bulbocavernosus

EYE CHART KEY
(hold at right angle to eye chart to keep from patient's view)

20/100	638
20/70	8745
20/50	63925
20/40	428365
20/30	374258
20/25	937826
20/20	428739